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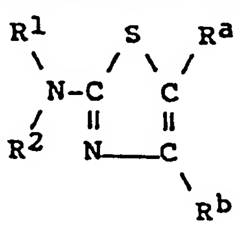
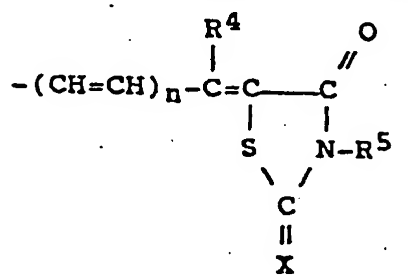
(54) Thiazole derivatives, their preparation and their use in the treatment of diabetes complications.

(57) Compounds of formula (I):



(I)

in which:
R^1 and R^2 are independently hydrogen, alkyl, aliphatic hydrocarbon groups having one or two carbon-carbon double or treble bonds, cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, alkanoyl, alkenoyl, cycloalkylcarbonyl, arylcarbonyl, substituted arylcaronyl, arylalkanoyl, substituted arylalkanoyl, arylalkenoyl, substituted arylalkenoyl, alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, aralkyloxycarbonyl, substituted aralkyloxycarbonyl, optionally substituted carbamoyl or thiocarbamoyl, alkylsulphonyl, haloalkylsulphonyl, arylsulphonyl, substituted arylsulphonyl, alkylthio, arylthio and substituted arylthio, or R^1 and R^2, together with the nitrogen atom to which they are attached, form a nitrogen-containing heterocyclic group; one of R^a and R^b is hydrogen, alkyl or halogen, and the other of R^a and R^b is a group of formula (II):



(II)

R^4 is hydrogen, carboxy, protected carboxy or optionally substituted carbamoyl; R^5 is hydrogen, or carboxyalkyl or protected carboxyalkyl in which the alkyl part is C_1-C_6; n = 0, 1 or 2; X is oxygen or sulphur;
are useful in the treatment of the complications attendant upon diabetes and may be prepared by condensation of a thiazolidine or rhodanine compound with a compound corresponding to the remainder of the molecule of the compound of formula (I).

Description

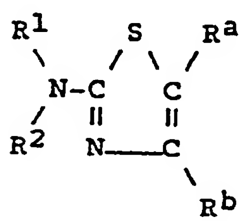
THIAZOLE DERIVATIVES, THEIR PREPARATION AND THEIR USE IN THE TREATMENT OF DIABETES COMPLICATIONS

The present invention relates to a series of new thiazole derivatives, in which the thiazole ring is attached via an unsaturated carbon chain to a rhodanine or thiazolidine-2,4-dione ring system. The invention also provides a process for preparing the novel compounds as well as methods and compositions for using them.

The enzyme, aldose reductase, is implicated in many of the complications of diabetes, and inhibitors of its activity can, therefore, be used in the treatment and prevention of such complications. A number of thiazolidine and/or rhodanine derivatives have been found to have the ability to inhibit the activity of aldose reductase. Thus, certain compounds of this type are disclosed in European Patent Publications No. 47,109 and 208,040, and in the published Japanese Patent Applications Kokai No. 56,175/86, 238,286/87 and 179,873/88 (the latter being published after the priority date hereof).

We have now discovered a new series of thiazole derivatives having a very marked ability to inhibit the activity of aldose reductase, which ability is believed to be significantly better than that of the above-mentioned prior art compounds, from which they differ structurally primarily by virtue of the thiazole group. Moreover, these new derivatives include compounds which, upon oral administration, have been found to combine excellent absorption from the gastro-intestinal tract with very low toxicity.

The compounds of the present invention are thiazole derivatives having the formula (I):



(I)

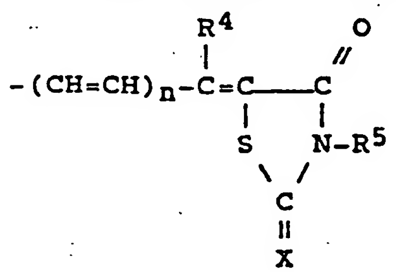
in which:

R^1 and R^2 are the same or different and each represents:

a hydrogen atom,
a C_1 - C_{12} alkyl group,
a C_3 - C_6 aliphatic hydrocarbon group having one or two carbon-carbon double or treble bonds,
a C_3 - C_8 cycloalkyl group,
a C_6 - C_{14} aryl group,
a substituted C_6 - C_{14} aryl group having at least one of substituents (a) defined below,
an aralkyl or substituted aralkyl group with from 1 to 3 aryl parts each of which is C_6 - C_{14} and an alkyl part which is C_1 - C_5, and said substituted aralkyl groups having at least one of substituents (a) defined below,
a C_1 - C_{12} alkanoyl group,
a C_3 - C_{12} alkenoyl group,
a C_4 - C_9 cycloalkylcarbonyl group,
a C_7 - C_{15} arylcarbonyl group,
a substituted C_7 - C_{15} arylcarbonyl group having at least one of substituents (a) defined below,
an arylalkanoyl group in which the aryl part is C_6 - C_{14} and is unsubstituted or has at least one of substituents (a) defined below and the alkanoyl part is C_2 - C_6,
an arylalkenoyl group in which the aryl part is C_6 - C_{14} and is unsubstituted or has at least one of substituents (a) defined below and the alkenoyl part is C_3 - C_6,
a C_2 - C_7 alkoxycarbonyl group,
a C_7 - C_{15} aryloxycarbonyl group,
a substituted C_7 - C_{15} aryloxycarbonyl group having at least one of substituents (a) defined below,
a C_8 - C_{20} aralkyloxycarbonyl group,
a substituted C_8 - C_{20} aralkyloxycarbonyl group having at least one of substituents (a) defined below,
a group of formula $-CONR^6R^7$,
a group of formula $-CSNR^6R^7$,
a C_1 - C_6 alkylsulphonyl group,
a C_1 - C_6 haloalkylsulphonyl group,
a C_6 - C_{14} arylsulphonyl group,
a substituted C_6 - C_{14} arylsulphonyl group having at least one of substituents (a) defined below,
a C_1 - C_6 alkylthio group,
a C_6 - C_{14} arylthio group, or
a substituted C_6 - C_{14} arylthio group having at least one of substituents (a) defined below;

or R^1 and R^2, together with the nitrogen atom to which they are attached, form a nitrogen-containing heterocyclic group having from 5 to 8 ring atoms, of which 0 or 1 are additional nitrogen and/or oxygen and/or

sulphur hetero-atoms, said heterocyclic group being unsubstituted or having at least one of substituents (b) defined below, or form such a heterocyclic group fused to at least one benzene or naphthalene ring system which ring system is unsubstituted or has at least one of substituents (c) defined below;
one of R^a and R^b represents a hydrogen atom, a C_1 - C_6 alkyl group or a halogen atom, and the other of R^a and R^b represents a group of formula (II):



(II)

R^4 represents a hydrogen atom, a carboxy group, a protected carboxy group or a group of formula -$CONR^8R^9$;
R^5 represents a hydrogen atom, or a carboxyalkyl or protected carboxyalkyl group in which the alkyl part is C_1 - C_6;
$\underline{n}$ = 0, 1 or 2;
$\underline{X}$ represents an oxygen or sulphur atom;
R^6 and R^7 are the same or different and each represents:
a hydrogen atom,
a C_1 - C_6 alkyl group,
a C_3 - C_6 alkenyl group,
a C_3 - C_8 cycloalkyl group,
a C_6 - C_{14} aryl group,
a substituted C_6 - C_{14} aryl group having at least one of substituents (c) defined below,
a C_7 - C_{19} aralkyl group,
a substituted C_7 - C_{19} aralkyl group having at least one of substituents (c) defined below,
a C_1 - C_6 alkylsulphonyl group,
a C_1 - C_6 haloalkylsulphonyl group,
a C_6 - C_{14} arylsulphonyl group,
a substituted C_6 - C_{14} arylsulphonyl group having at least one of substituents (c) defined below,
a C_1 - C_{12} alkanoyl group,
a C_4 - C_9 cycloalkylcarbonyl group,
a C_7 - C_{15} arylcarbonyl group,
a substituted C_7 - C_{15} arylcarbonyl group having at least one of substituents (c) defined below;
R^8 and R^9 are the same or different and each represents a hydrogen atom or a C_1 - C_6 alkyl group;

<u>substituents (a):</u>
C_1 - C_6 alkyl groups,
C_1 - C_6 haloalkyl groups,
C_6 - C_{14} aryl groups,
C_7 - C_{19} aralkyl groups,
C_1 - C_{12} alkanoyl groups,
C_7 - C_{15} arylcarbonyl groups,
C_2 - C_7 alkoxycarbonyl groups,
C_7 - C_{15} aryloxycarbonyl groups,
C_8 - C_{20} aralkyloxycarbonyl groups,
groups of formula -$CONR^{10}R^{11}$,
groups of formula -$CSNR^{10}R^{11}$,
(where R^{10} and R^{11} are the same or different and each represents a hydrogen atom, a C_1 - C_6 alkyl group or a C_6 - C_{14} aryl group),
groups of formula -$NR^{12}R^{13}$,
(where R^{12} and R^{13} are the same or different and each represents a hydrogen atom, a C_1 - C_6 alkyl group, a C_6 - C_{14} aryl group, a C_1 - C_6 alkanoyl group or a C_7 - C_{15} arylcarbonyl group),
halogen atoms,
nitro groups,
cyano groups,
hydroxy groups,
C_1 - C_6 alkoxy groups,
C_6 - C_{14} aryloxy groups,
C_1 - C_{12} alkanoyloxy groups,
C_7 - C_{15} arylcarbonyloxy groups,

C_2 - C_7 alkoxycarbonyloxy groups,
C_7 - C_{15} aryloxycarbonyloxy groups,
C_8 - C_{20} aralkyloxycarbonyloxy groups,
carboxy groups,
sulpho groups, and
sulphamoyl groups;

substituents (b):
oxygen atoms (i.e. to form an oxo group),
halogen atoms,
C_1 - C_6 alkyl groups,
C_6 - C_{14} aryl groups,
substituted C_6 - C_{14} aryl groups having at least one of substituents (c) defined below,
C_7 - C_{19} aralkyl groups,
substituted C_7- C_{19} aralkyl groups having at least one of substituents (c) defined below,
C_1 - C_6 alkanoyl groups,
C_7 - C_{15} arylcarbonyl groups, and
substituted C_7 - C_{15} arylcarbonyl groups having at least one of substituents (c) defined below;

substituents (c):
C_1 - C_4 alkyl groups,
C_1 - C_4 alkoxy groups,
C_6 - C_{10} aryl groups,
C_6 - C_{10} aryloxy groups,
C_1 - C_6 alkanoyloxy groups,
halogen atoms,
hydroxy groups,
cyano groups,
trifluoromethyl groups,
carboxy groups, and
nitro groups.

The invention also embraces the pharmaceutically acceptable salts of said compounds of formula (I) and, where said compounds contain a carboxy group, also the esters thereof.

The invention further provides a pharmaceutical composition for the treatment or prevention of complications of diabetes, which comprises at least one compound of said formula (I) or a pharmaceutically acceptable salt or ester thereof in admixture with a pharmaceutically acceptable carrier or diluent.

The invention still further provides the use for the manufacture of a medicament for the treatment or prophylaxis of the complications of diabetes in a mammal (which may be human or non-human) suffering from diabetes of at least one compound of said formula (I) or a pharmaceutically acceptable salt or ester thereof.

The invention also provides processes for preparing the aforesaid compounds, as will be described in detail hereafter.

In the compounds of the present invention, where R^1 and/or R^2 represents an alkyl group, this may be a straight or branched chain alkyl group having from 1 to 12 carbon atoms, and examples include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, sec-butyl, pentyl, isopentyl, neopentyl, 2-methylbutyl, 1,1-dimethylpropyl, 1-ethylpropyl, hexyl, isohexyl, neohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,3-dimethylbutyl, 2-ethylbutyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, heptyl, 1,1-dimethylpentyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 1-propylbutyl, 1-ethylpentyl, 1-isopropyl-2-methylpropyl, 2-ethylpentyl, octyl, 1-methylheptyl, 1,5-dimethylhexyl, 1-ethylhexyl, 1-ethyl-3-methylpentyl, 1,1,3,3-tetramethylbutyl, 2-methyloctyl, nonyl, 2-methylnonyl, 2-ethyloctyl, decyl, 2-methyldecyl, 2-ethyldecyl, undecyl and dodecyl groups. Of these, we prefer the C_1 - C_8 alkyl groups, of which the C_1 - C_6 alkyl groups, for example the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, sec-butyl, pentyl, isopentyl, neopentyl, 2-methylbutyl, 1,1-dimethylpropyl, 1-ethylpropyl, hexyl, isohexyl, neohexyl, 1-methylpentyl, 3-methylpentyl, 1,3-dimethylbutyl, 2-ethylbutyl, 1,2,2-trimethylpropyl and 1-ethyl-1-methylpropyl groups are more preferred. The C_1 - C_4 alkyl groups, for example the methyl, ethyl, propyl, isopropyl, butyl, isobutyl and sec-butyl groups are most preferred.

Where R^1 and/or R^2 represents an aliphatic hydrocarbon group having one or two carbon-carbon double or treble bonds, this may be an alkenyl group, which may be a straight or branched chain alkenyl group having from 3 to 6 carbon atoms, and examples include the allyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-pentenyl, 3-methyl-2-butenyl, 2,4-pentadienyl, 2-propylallyl, 2,3-dimethyl-2-butenyl, 2-methyl-2-propenyl, 2-methyl-3-pentenyl, 4-methyl-3-pentenyl, 1-methyl-4-pentenyl, 5-hexenyl, 4-hexenyl, 3-hexenyl, 2-hexenyl and 2,4-hexadienyl groups, of which the allyl and 2-methyl-2-propenyl groups are preferred.

Alternatively, the aliphatic hydrocarbon group having one or two carbon-carbon double or treble bonds represented by R^1 and/or R^2 may be an alkynyl group, which may be a straight or branched chain alkynyl group having from 3 to 6 carbon atoms, and examples include the propargyl, 2-butynyl, 3-butynyl, 1,1-dimethyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-methyl-2-butynyl, 2-hexynyl, 1-methyl-2-pentynyl, 1-methyl-3-pen-

tynyl, 1,1-dimethyl-2-butynyl and 1,1-dimethyl-3-butynyl groups, of which the propargyl group is preferred.

Where R^1 and/or R^2 represents a cycloalkyl group, this has from 3 to 8 carbon atoms and examples include the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl groups, of which the C_3 - C_6 cycloalkyl groups are preferred.

Where R^1 and/or R^2 represents an aryl group, this is a carbocyclic aromatic group which has from 6 to 14 carbon atoms in the aromatic ring system and examples include the phenyl, 1-naphthyl, 2-naphthyl, 1-anthryl, 2-anthryl and 9-anthryl groups, any of which may be unsubstituted or may have at least one of substituents (a), defined above and exemplified below, of which the phenyl and naphthyl groups are more preferred and the phenyl group is most preferred.

Specific examples of substituted aryl groups which may be represented by R^1 and/or R^2 include the o-, m- or p-aminophenyl, o-, m- or p-(N,N-dimethylamino)phenyl, o-, m-, or p-nitrophenyl, o-, m- or p-fluorophenyl, o-, m- or p-chlorophenyl, o-, m- or p-bromophenyl, o-, m- or p-cyanophenyl, o-, m- or p-hydroxyphenyl o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m- or p-ethoxycarbonylphenyl, o-, m- or p-ethylcarbamoylphenyl, o-, m- or p-pentyloxyphenyl, o-, m- or p-phenoxyphenyl, o-, m- or p-formyloxyphenyl, o-, m- or p-acetoxy phenyl, o-, m- or p-acetamidophenyl, o-, m- or p-carboxyphenyl, o-, m- or p-benzoylaminophenyl, o-, m- or p-ethyl aminophenyl, o-, m- or p-phenylaminophenyl, o-, m- or p-benzoyloxyphenyl, o-, m- or p-benzoylphenyl, o-, m- or p-acetylphenyl, o-, m- or p-carbamoylphenyl, o-, m- or p-sulphamoylphenyl, o-, m- or p-methylphenyl, o-, m- or p-ethylphenyl o-, m- or p-isopropylphenyl o-, m- or p-biphenyl, o-, m- or p-benzyloxyphenyl, o-, m- or p-trifluoromethylphenyl, 4-fluoro-3-nitrophenyl, 2-bromo-4-methylphenyl, 2-bromo-4,6-difluorophenyl 2-acetamido-5-trifluoromethylphenyl, 2-ethoxy-4-fluoro-6-nitrophenyl, pentafluorophenyl, 2,4-dibromophenyl, 2,4-difluorophenyl, 2,4,6-tribromophenyl 4-iodophenyl 2,3-dimethoxyphenyl, 2,4-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 2,6-dimethylphenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 2,5-dichlorophenyl, 2,4,6-trichlorophenyl, 2,4,6-trifluorophenyl 2,4,5-trifluorophenyl, 2-hydroxy-3,5-dibromophenyl, 2-chloro-4-fluorophenyl, 2-fluoro-4-trifluoromethylphenyl, 2-nitro-4-trifluoromethylphenyl, 2-fluoro-4-chlorophenyl, 4-fluoro-2-trifluoromethylphenyl, 2-hydroxy-3,5-di-t-butylphenyl, 4-hydroxy-3,5-di-t-butylphenyl, 4-hydroxy-3,5-dimethylphenyl, 3,5-dichloro-4-hydroxyphenyl, 2-hydroxy-5-(1,1,3,3-tetramethylbutyl)phenyl, 4-fluoro-1-naphthyl, 4-chloro-1-naphthyl, 4-fluoro-2-naphthyl, 4-chloro-2-naphthyl, 3-hydroxy-2-naphthyl and 4-sulpho-1-naphthyl groups.

Where R^1 and/or R^2 represents an aralkyl group, the aryl part of this group is a carbocyclic aromatic group which has from 6 to 14 carbon atoms in the aromatic ring system and the aralkyl group may contain from 1 to 3 such aryl groups. The alkyl part is a C_1 - C_5, preferably C_1 - C_3, more preferably C_1 - C_2, alkyl group, which may be any of those alkyl groups having from 1 to 5 carbon atoms exemplified above in relation to the alkyl groups which may be represented by R^1 and R^2. The aralkyl group may be unsubstituted or it may have, preferably on its aromatic ring, at least one of substituents (a), defined above and exemplified in general terms below. It preferably has a total of from 7 to 19 carbon atoms including the atoms of both the aromatic ring system and the alkyl part [and excluding any carbon atoms in the substituent(s) (a)], but the number will depend, inter alia, on the nature and number of the aryl groups; the number of aryl groups may be restricted by steric constraints. Examples of the unsubstituted aralkyl groups include the benzyl, 1-phenylethyl, 2-phenylethyl (commonly referred to as "phenethyl"), 1-phenylpropyl, 3-phenylpropyl, 1-phenylbutyl, 4-phenylbutyl, 1-methyl-1-phenylethyl, 1-naphthylmethyl, 2-naphthylmethyl, bis(2-naphthyl)methyl, (1-naphthyl)(phenyl)methyl, 9-anthrylmethyl, diphenylmethyl and triphenylmethyl groups. Examples of the substituted groups include those in which the aryl group of any of the above aralkyl groups is replaced by one of the substituted aryl groups listed above, especially the bis(p-fluorophenyl)methyl and (2-naphthyl)(p-fluorophenyl)methyl groups.

Where R^1 and/or R^2 represents an alkanoyl group having from 1 to 12 carbon atoms, this may be a straight or branched chain group, for example a formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, hexanoyl, heptanoyl, octanoyl, nonanoyl or dodecanoyl group, of which the C_1 - C_6 alkanoyl groups are preferred.

Where R^1 and/or R^2 represents an alkenoyl group having from 3 to 12 carbon atoms, this may be a straight or branched chain group, for example an acryloyl, methacryloyl, crotonoyl, isocrotonyl, oleoyl or elaidoyl group.

Where R^1 and/or R^2 represents an alicyclic acyl group having from 4 to 9 carbon atoms, i.e. a cycloalkylcarbonyl group, the cycloalkyl part has from 3 to 8 ring carbon atoms and may be any of the cycloalkyl groups exemplified above.. Examples include the cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, cycloheptylcarbonyl and cyclooctylcarbonyl groups.

Where R^1 and/or R^2 represents an aromatic acyl group having from 7 to 15 carbon atoms, this is an arylcarbonyl group, in which the aryl part is C_6 - C_{14} and the aryl part may be unsubstituted or may have at least one of substituents (a), defined above and exemplified below; the aryl part may be any of the substituted and unsubstituted aryl groups exemplified above. The benzoyl and substituted benzoyl groups are preferred. Specific examples include the benzoyl, 1-naphthoyl 2-naphthoyl 9-anthracenecarbonyl o-, m- or p-fluorobenzoyl, o-, m- or p-chlorobenzoyl, o-, m- or p-bromobenzoyl, o-, m- or p-methylbenzoyl, o-, m- or p-ethylbenzoyl, o-, m- or p-nitrobenzoyl, o-, m- or p-cyanobenzoyl, o-, m- or p-carboxybenzoyl, o-, m- or p-ethoxycarbonylbenzoyl, o-, m- or p-hydroxybenzoyl, o-, m- or p-methoxybenzoyl, o-, m- or p-ethoxybenzoyl, o-, m- or p-formyloxybenzoyl, o-, m- or p-acetoxybenzoyl, o-, m- or p-phenoxybenzoyl, o-, m- or p-carbamoylbenzoyl, o-, m- or p-sulphamoylbenzoyl, o-, m- or p-trifluoromethylbenzoyl, o-, m- or p-benzoylbenzoyl, o-, m- or p-phenylbenzoyl, o-, m- or p-aminobenzoyl, o-, m- or p-acetamidobenzoyl, o-, m- or p-benzoylaminobenzoyl, 2,4-dichlorobenzoyl, 3,4-dichlorobenzoyl, 2,5-dichlorobenzoyl, pentafluorobenzoyl, 3,4,5-trimethoxybenzoyl,

4-hydroxy-3,5-di-t-butylbenzoyl, 2,3-dibromobenzoyl, 3,5-dibromobenzoyl, 3,5-dinitrobenzoyl, 3-nitro-2-naphthoyl and 3-hydroxy-2-anthracenecarbonyl groups.

Where R^1 and/or R^2 represents an arylalkanoyl group in which the aryl part is C_6 - C_{14} and is unsubstituted or has at least one of substituents (a) and the alkanoyl part is C_2 - C_6, or an arylalkenoyl group in which the aryl part is C_6 - C_{14} and is unsubstituted or has at least one of substituents (a) and the alkenoyl part is C_3 - C_6, the aryl, alkanoyl and alkenoyl parts may be as exemplified above. The aryl part is preferably phenyl. Specific examples of such groups include the phenylacetyl, 3-phenylpropionyl, 4-phenylbutyryl, 5-phenylvaleryl, 6-phenylhexanoyl, hydratropoyl, atropoyl and cinnamoyl groups, and such groups in which the phenyl group has at least one of substituents (a).

Where R^1 and/or R^2 represents an alkoxycarbonyl group, this may be a straight or branched chain group having, in total, from 2 to 7 carbon atoms and examples include the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, t-butoxycarbonyl, sec-butoxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl, neopentyloxycarbonyl, hexyloxycarbonyl and isohexyloxycarbonyl groups.

Where R^1 and/or R^2 represents an aryloxycarbonyl group, the aryl part may be substituted or unsubstituted and has from 6 to 14 carbon atoms in the aromatic ring. Examples include those in which the aryl group is any one of those aryl groups exemplified above in relation to the aryl groups which may be represented by R^1 and R^2, preferably phenyl or naphthyl. Specific examples of such groups include the phenoxycarbonyl, 1-naphthyloxycarbonyl and 2-naphthyloxycarbonyl groups,, as well as such groups having at least one of substituents (a), defined above and exemplified below.

Where R^1 and/or R^2 represents an aralkyloxycarbonyl group, this has, in total, from 8 to 20 carbon atoms, i.e. 1 carbon atom provided by the carbonyl group and from 7 to 19 provided by the aralkyl part. The aralkyl part may be substituted or unsubstituted and may be any one of those aralkyl groups having from 7 to 19 carbon atoms exemplified above in relation to the aralkyl groups which may be represented by R^1 and R^2. Specific examples of such groups include the benzyloxycarbonyl, 1-phenylethoxycarbonyl, 2-phenylethoxycarbonyl, 1-phenylpropoxycarbonyl, 4-phenylbutoxycarbonyl, 1-methyl-1-phenylethoxycarbonyl, 2-naphthylmethoxycarbonyl, 9-anthrylmethoxycarbonyl and diphenylmethoxycarbonyl groups.

Where R^1 and/or R^2 represents a group of formula $-CONR^6R^7$ or a group of formula $-CSNR^6R^7$, the groups represented by R^6 and R^7 include: hydrogen atoms, C_1 - C_6 alkyl groups, C_3 - C_6 alkenyl groups, C_3 - C_8 cycloalkyl groups, C_7 - C_{19} aralkyl groups, C_6 - C_{14} aryl groups which may be substituted or unsubstituted, and, if substituted, have at least one of substituents (c), C_1 - C_6 alkylsulphonyl groups, C_6 - C_{14} arylsulphonyl groups which may be substituted or unsubstituted, and, if substituted, have at least one of substituents (c), C_1 - C_6 haloalkanesulphonyl groups, C_1 - C_{12} alkanoyl groups, C_4 - C_9 cycloalkylcarbonyl groups, C_7 - C_{15} arylcarbonyl groups and substituted C_7 - C_{15} arylcarbonyl groups, which may be any of those groups exemplified in relation to the groups which may be represented by R^1 and R^2. Examples of such carbamoyl groups include the methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, isobutylcarbamoyl, sec-butylcarbamoyl, t-butylcarbamoyl, 1-ethylpropylcarbamoyl, pentylcarbamoyl, hexylcarbamoyl, dimethylcarbamoyl, N-butyl-N-methylcarbamoyl, N-ethyl-N-hexylcarbamoyl, allylcarbamoyl, cyclohexylcarbamoyl, phenylcarbamoyl, 1-naphthylcarbamoyl, diphenylcarbamoyl, N-methyl-N-phenylcarbamoyl, o-, m- and p-nitrophenylcarbamoyl, o-, m- andp-fluorophenylcarbamoyl, o-, m- and p-chlorophenylcarbamoyl, o-, m- and p-bromophenylcarbamoyl, o-, m- andp-trifluoromethylphenylcarbamoyl, o-, m- and p-hydroxyphenylcarbamoyl, o-, m- and p-methoxyphenylcarbamoyl, o-, m- and p-ethoxyphenylcarbamoyl, o-, m- and p-phenoxyphenylcarbamoyl, o-, m- and p-formyloxyphenylcarbamoyl, o-, m- and p-acetoxyphenylcarbamoyl, o-, m- and p-carboxyphenylcarbamoyl, o-, m- and p-methylphenylcarbamoyl, o-, m- and p-ethylphenylcarbamoyl, o-, m-and p-isopropylphenylcarbamoyl, o-, m- and p-biphenylcarbamoyl, 2-bromo-4-methylphenylcarbamoyl, 2,4-difluorophenylcarbamoyl, 2,4-dibromophenylcarbamoyl, 4-fluoro-3-nitrophenylcarbamoyl, 2,6-dimethylphenylcarbamoyl, 2,4,6-trifluorophenylcarbamoyl, 2,4-6-tribromophenylcarbamoyl, 4-iodophenylcarbamoyl, 2,3-dimethoxyphenylcarbamoyl, 2,4-dimethoxyphenylcarbamoyl, 3,4-dimethoxyphenylcarbamoyl, 3,4,5-trimethoxyphenylcarbamoyl, 2,4-dichlorophenylcarbamoyl, 3,4-dichlorophenylcarbamoyl, 2,4,6-trichlorophenylcarbamoyl, 2-hydroxy-3,5-dibromophenylcarbamoyl 2-hydroxy-3,5-di-t-butylphenylcarbamoyl, 4-hydroxy-3,5-di-t-butylphenylcarbamoyl, 4-hydroxy-3,5-dichlorophenylcarbamoyl, 3-hydroxy-2-naphthylcarbamoyl, benzylcarbamoyl, 4-phenylbutylcarbamoyl, 2-phenylethylcarbamoyl, 1-naphthylmethylcarbamoyl, methanesulphonylcarbamoyl, trifluoromethanesulphonylcarbamoyl, benzenesulphonylcarbamoyl, 4-methylbenzenesulphonylcarbamoyl, benzoylcarbamoyl, acetylcarbamoyl and cyclopentylcarbonylcarbamoyl groups.

Examples of such thiocarbamoyl groups include the methyl(thiocarbamoyl), ethyl(thiocarbamoyl), propyl(thiocarbamoyl), isopropyl(thiocarbamoyl), butyl(thio carbamoyl), isobutyl(thiocarbamoyl), sec-butyl(thiocarbamoyl), t-butyl(thiocarbamoyl), 1-ethylpropyl(thiocarbamoyl), pentyl(thiocarbamoyl), hexyl(thiocarbamoyl), dimethyl(thiocarbamoyl), N-butyl-N-methyl(thiocarbamoyl), N-hexyl-N-ethyl(thiocarbamoyl), allyl(thiocarbamoyl), cyclohexyl(thiocarbamoyl), phenyl(thiocarbamoyl), 1-naphthyl(thiocarbamoyl), N,N-diphenyl(thiocarbamoyl), N-methyl-N-phenyl(thiocarbamoyl), o-, m- and p-nitrophenyl(thiocarbamoyl), o-, m- and p-fluorophenyl(thiocarbamoyl), o-, m- and p-chlorophenyl(thiocarbamoyl), o-, m-and p- bromophenyl(thiocarbamoyl), o-, m- and p-trifluoromethylphenyl(thiocarbamoyl), o-, m- and p-hydroxyphenyl(thiocarbamoyl), o-, m- and p-methoxyphenyl(thiocarbamoyl, o-, m- and p-ethoxyphenyl(thiocarbamoyl), o-, m- and p-phenoxyphenyl(thiocarbamoyl), o-, m- and p-formyloxyphenyl (thiocarbamoyl), o-, m- and p-acetoxyphenyl(thiocarbamoyl), o-, m- and p-carboxyphenyl(thiocarbamoyl), o-, m- and p-methylphenyl(thiocarbamoyl),

o-, m- and p-ethylphenyl (thiocarbamoyl), o-, m- and p-isopropylphenyl(thiocarbamoyl), o-, m- and p-biphenyl(thiocarbamoyl), 2-bromo-4-methylphenyl(thiocarbamoyl), 2,4-difluorophenyl(thiocarbamoyl), 2,4-dibromophenyl(thiocarbamoyl), 2,4,6-trifluorophenyl(thiocarbamoyl), 2,4,6-tribromophenyl(thiocarbamoyl),. 4-iodophenyl(thiocarbamoyl), 2,3-dimethoxyphenyl(thiocarbamoyl), 2,4-dimethoxyphenyl(thiocarbamoyl), 3,4-dimethoxyphenyl(thiocarbamoyl), 3,4,5-trimethoxyphenyl(thiocarbamoyl), 2,4-dichlorophenyl(thiocarbamoyl) < 3,4-dichlorophenyl(thiocarbamoyl), 2,4,6-trichlorophenyl(thiocarbamoyl), 2-hydroxy-3,5-dibromophenyl(thiocarbamoyl), 2-hydroxy-3,5-di-t-butylphenyl(thiocarbamoyl), 4-hydroxy-3,5-di-t-butylphenyl(thiocarbamoyl), 4-hydroxy-3,5-dichlorophenyl(thiocarbamoyl), 3-hydroxy-2-naphthyl(thiocarbamoyl), benzyl(thiocarbamoyl), 4-phenylbutyl(thiocarbamoyl), 2-phenylethyl(thiocarbamoyl), 1-naphthylmethyl(thiocarbamoyl), methanesulphonyl(thiocarbamoyl), trifluoro methanesulphonyl(thiocarbamoyl), benzenesulphonyl(thiocarbamoyl), 4-methylbenzenesulphonyl(thiocarbamoyl), benzoyl(thiocarbamoyl), acetyl(thiocarbamoyl) and cyclopentylcarbonyl(thiocarbamoyl) groups.

Preferably, R^6 and R^7 represent hydrogen atoms, C_1 - C_6 alkyl groups, C_3 - C_6 alkenyl groups, C_3 - C_8 cycloalkyl groups, C_6 - C_{14} aryl groups, substituted C_6 - C_{14} aryl groups having C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen, trifluoromethyl and/or nitro groups as substituents, benzyl groups, benzenesulphonyl groups, toluenesulphonyl groups, C_2 - C_6 alkanoyl groups or C_7 - C_{11} arylcarbonyl groups. More preferably, they represent hydrogen atoms, C_1 - C_6 alkyl groups, allyl groups, cyclohexyl groups, C_6 - C_{10} aryl groups, substituted C_6 - C_{14} aryl groups having C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen, trifluoromethyl and/or nitro groups as substituents, benzenesulphonyl groups, toluenesulphonyl groups or benzoyl groups.

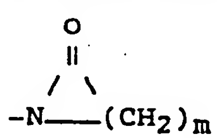
The most highly preferred groups of formula $-CONR^6R^7$ and $-CSNR^6R^7$ are those wherein R^6 is a hydrogen atom and R^7 is a C_6 - C_{10} aryl group, or a C_6 - C_{10} aryl group substituted with C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen, trifluoromethyl and/or nitro substituents.

However, it is preferred that, when R^6 represents one of these sulphonyl or acyl groups, R^7 should represent a group or atom other than the sulphonyl or acyl group represented by R^6.

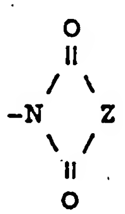
Where R^1 and/or R^2 represents a C_1 - C_6 alkylsulphonyl group, a C_1 - C_6 haloalkylsulphonyl group, a C_6 - C_{14} arylsulphonyl group or a substituted C_6 - C_{14} arylsulphonyl group, the alkyl, haloalkyl and aryl parts of these groups may be as exemplified for the corresponding groups represented by R^1 and R^2 or substituents (a). The haloalkyl group preferably has from 1 to 4 carbon atoms, and the aryl group preferably has from 6 to 10 carbon atoms. Specific examples of such sulphonyl groups include the methanesulphonyl, trifluoromethanesulphonyl,, benzenesulphonyl and p-toluenesulphonyl groups.

Where R^1 and/or R^2 represents an alkylthio group or an arylthio group which may be substituted or unsubstituted, the alkyl and aryl parts are as generally exemplified above. The alkylthio group has from 1 to 6 carbon atoms and the aryl group preferably has from 6 to 10 carbon atoms. Examples of such groups include the methylthio, ethylthio, butylthio, hexylthio, phenylthio and tolylthio groups.

Where R^1 and R^2 together with the nitrogen atom to which they are attached form a nitrogen-containing heterocyclic group as defined above, this preferably has 5 or 6 ring atoms, and may be unsubstituted or may have at least one of the substituents (b); and when they form such a heterocyclic group fused to at least one benzene or naphthalene ring system, this is preferably a benzene ring system, and may be unsubstituted or may have at least one of the substituents (c). Examples of such heterocyclic groups include the 1-pyrrolidinyl, piperidino hexamethyleneimino, heptamethyleneimino, morpholino, thiazolidin-3-yl, thiomorpholino, 1-homopiperazinyl, and 1-piperazinyl and 4-substituted-1-piperazinyl groups (wherein the 4-substituent is a C_1 - C_4 alkyl, phenyl, benzyl, benzoyl or C_1 - C_6 alkanoyl group), as well as groups of formula:



(wherein m is an integer of from 3 to 5), and groups of formula:



[wherein Z represents, for example, an ethylene, trimethylene, 1,2-phenylene, 4-carboxy-1,2-phenylene, 3,4,5,6-tetrabromo-1,2-phenylene, 1,8-naphthylene, 4-chloro-1,8-naphthylene, 2,2'-biphenyldiyl, vinylene or 1,2-dichlorovinylene group, or a group of formula $-C(CH_3)=C(CH_3)-$].

The preferred heterocyclic groups are the 1-pyrrolidinyl, piperidine, hexamethyleneimino, morpholino, thiomorpholino, 1-homopiperazinyl, 1-piperazinyl, and 1-piperazinyl groups substituted at the 4-position with C_1 - C_4 alkyl, phenyl, acetyl or benzoyl groups.

However, it is preferred that R^2 should represent a group other than the above-mentioned acyl, sulphonyl and thio groups represented by R^1, when R^1 represents an alkanoyl, alkenoyl, cycloalkylcarbonyl, arylcarbonyl, substituted arylcarbonyl, arylalkanoyl, substituted arylalkanoyl, arylalkenoyl, substituted arylalkenoyl, alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, aralkyloxycarbonyl, substituted aralkyloxycarbonyl, groups of formula -CONR^{6}R^7 and -CSNR^{6}R^7, alkylsulphonyl, arylsulphonyl, substituted arylsulphonyl, alkylthio, arylthio or substituted arylthio.

Where R^a or R^b represents an alkyl group, this may be a straight or branched chain alkyl group having from 1 to 6 carbon atoms, and examples include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, sec-butyl, pentyl, isopentyl, neopentyl, 2-methylbutyl, 1-ethylpropyl, hexyl, isohexyl, neohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,3-dimethylbutyl and 2-ethylbutyl groups.

Where R^a or R^b represents a halogen atom, this may be a fluorine, chlorine, bromine or iodine atom, preferably a chlorine atom or a bromine atom.

However, we prefer that R^a should represent a hydrogen atom, an alkyl group or a halogen atom and R^b should represent a group of formula (II), and more prefer that R^a should represent a hydrogen atom.

Where R^4 represents a protected carboxy group, this may be any such group commonly used in compounds of this type, e.g. to form a pharmaceutically acceptable ester group. The precise nature of such a group is not critical to the invention, except that, where the compound is to be used as a medicine, it should be pharmaceutically acceptable. Where the compound is to be used for some other purpose, e.g. as an intermediate in the preparation of another compound, even this limitation does not apply. Examples of such protected carboxy groups include:-

straight and branched chain alkoxycarbonyl groups in which the alkyl part is a C_1 - C_8 alkyl group, more preferably a C_1 - C_4 alkyl group, such as those exemplified in relation to R^1 and R^2, but most preferably the alkoxycarbonyl groups having from 2 to 5 carbon atoms, such as the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, sec-butoxycarbonyl, isobutoxycarbonyl and t-butoxycarbonyl groups;

halogenated C_1 - C_6, preferably C_1 - C_4, alkoxycarbonyl groups in which the alkyl part is as defined and exemplified in relation to the alkyl groups which may be represented by R^1 and R^2, and the halogen atom is chlorine, fluorine, bromine or iodine, such as the 2,2,2-trichloroethoxycarbonyl, 2-haloethoxycarbonyl (e.g. 2-chloroethoxycarbonyl, 2-fluoroethoxycarbonyl, 2-bromoethoxycarbonyl or 2-iodoethoxycarbonyl), 2,2-dibromoethoxycarbonyl and 2,2,2-tribromoethoxycarbonyl groups;

straight and branched chain alkenyloxycarbonyl and alkadienyloxycarbonyl groups having from 4 to 7 carbon atoms, such as the allyloxycarbonyl, 3-methyl-2-butenyloxycarbonyl, 2-chloroallyloxycarbonyl, 2-methylallyloxycarbonyl and 2,4-hexadienyloxycarbonyl groups;

cycloalkyloxycarbonyl groups having from 4 to 9 carbon atoms, such as the cyclopropyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl and cyclooctyloxycarbonyl groups;

aryloxycarbonyl groups having from 7 to 15 carbon atoms, such as the phenoxycarbonyl, 1-naphthyloxycarbonyl, 2-naphthyloxycarbonyl and 1-anthryloxycarbonyl groups, and such groups having at least one carboxylic acylamino substituent and/or at least one of the substituents (c) defined above, for example the p-chlorophenoxycarbonyl, p-bromophenoxycarbonyl, m-nitrophenoxycarbonyl, o-carboxyphenoxycarbonyl, p-carbamoylphenoxycarbonyl, p-formyloxyphenoxycarbonyl, 2,4-dichlorophenoxycarbonyl, 3,4-dichlorophenoxycarbonyl, 2,4-dibromophenoxycarbonyl, o, m- or p-tolyloxycarbonyl and benzamidophenoxycarbonyl groups, of which phenoxycarbonyl groups which may be unsubstituted or substituted are preferred;

aralkyloxycarbonyl groups in which the aralkyl group has from 7 to 19 carbon atoms, and whose alkyl moiety is straight or branched, which may be unsubstituted or may have at least one methylenedioxy substituent and/or at least one of substituents (c) defined above, such as the benzyloxycarbonyl, 2-phenylethoxycarbonyl, 4-phenylbutoxycarbonyl, 2-naphthylmethoxycarbonyl, 1-phenylbutoxycarbonyl, 1-phenylethoxycarbonyl, 3-phenylpropoxycarbonyl, 2-phenylpropoxycarbonyl, 1-naphthylmethoxycarbonyl, 2-naphthylmethoxycarbonyl, 2-(1-naphthyl)ethoxycarbonyl, 2-(2-naphthyl)ethoxycarbonyl, benzhydryloxycarbonyl (i.e. diphenylmethoxycarbonyl), triphenylmethoxycarbonyl, bis(o-nitrophenyl)methoxycarbonyl, 9-anthrylmethoxycarbonyl, 2,4,6-trimethylbenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 3-nitrobenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl and piperonyloxycarbonyl groups, of which benzyloxycarbonyl groups, which may be unsubstituted or substituted are preferred;

phenacyloxycarbonyl groups, which may be unsubstituted or have at least one of substituents (a) defined and exemplified above, for example the phenacyloxycarbonyl group itself or the p-bromophenacyloxycarbonyl group;

geranyloxycarbonyl groups;

1-(aliphatic acyloxy)C_1 - C_4 alkoxycarbonyl groups, in which the acyl group is preferably an alkanoyl or a cycloalkylcarbonyl group, and is more preferably a C_2 - C_6 alkanoyl or a C_4 - C_7 cycloalkylcarbonyl group, such as the acetoxymethoxycarbonyl, 1-acetoxyethoxycarbonyl, propionyloxymethoxycarbonyl, butyryloxymethoxycarbonyl, isobutyryloxymethoxycarbonyl, pivaloyloxymethoxycarbonyl, 1-pivaloyloxyethoxycarbonyl and cyclohexylcarbonyloxymethoxycarbonyl groups;

1-(alkoxycarbonyloxy) C_1 - C_4 alkoxycarbonyl groups, in which the alkoxy part is C_1 - C_6, preferably C_1 - C_4, such as the methoxycarbonyloxymethoxycarbonyl, 1-methoxycarbonyloxyethoxycarbonyl, 1-ethoxycarbonyloxyethoxycarbonyl, 1-propoxycarbonyloxyethoxycarbonyl, 1-isopropoxycarbonyloxyethoxycarbonyl, 1-butoxycarbonyloxyethoxycarbonyl and 1-isobutoxycarbonyloxyethoxycarbonyl groups;

alkoxymethoxycarbonyl groups, in which the alkoxy part is C_1 - C_6, preferably C_1 - C_4, and may itself be substituted by a single unsubstituted alkoxy group, such as the methoxymethoxycarbonyl, ethoxymethoxycarbonyl, propoxymethoxycarbonyl, isopropoxymethoxycarbonyl, butoxymethoxycarbonyl and methoxyethoxymethoxycarbonyl groups; and
other groups capable of being hydrolyzed in vivo under physiological conditions (which include e.g. the pivaloyloxymethoxycarbonyl, acetoxymethoxycarbonyl and methoxymethoxycarbonyl groups referred to above) as well as, for example, the phthalidyl, phthalidyloxycarbonyl, indanyloxycarbonyl, (2-oxo-5-methyl-1,3-dioxolen-4-yl)methoxycarbonyl and (2-oxo-5-phenyl-1,3-dioxolen-4-yl)methoxycarbonyl groups.

Of the protected carboxy groups, alkoxycarbonyl groups and benzyloxycarbonyl groups are preferred and alkoxycarbonyl groups are more preferred.

Where R^4 represents a group of formula $-CONR^8R^9$, this is a substituted or unsubstituted carbamoyl group, and the alkyl groups which may be represented by R^8 and R^9 may be any of those having from 1 to 6 carbon atoms exemplified above. Examples include the carbamoyl, methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, sec-butylcarbamoyl, isobutylcarbamoyl, t-butylcarbamoyl, pentylcarbamoyl, hexylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl and N-butyl-N-methylcarbamoyl.

However, R^4 most preferably represents a hydrogen atom or a protected carboxy group.

Where R^5 represents a carboxyalkyl group, the alkyl part of this may be a straight or branched chain alkyl group having from 1 to 6, preferably from 1 to 3, carbon atoms (and more preferably one carbon atom), and a carboxy substituent, and examples include the carboxymethyl, 1-carboxyethyl, 2-carboxyethyl, 3-carboxypropyl, 1-carboxy-1-methylethyl, 1-carboxypropyl, 2-carboxyphenyl, 4-carboxybutyl, 3-carboxy-2-methylpropyl, 1-carboxypentyl, 5-carboxypentyl and 6-carboxyhexyl groups.

Where R^5 represents a protected carboxyalkyl group, the carboxyalkyl group itself may be as defined and exemplified above, and the protecting group for the carboxy group may be any of those protecting groups forming part of the protected carboxy group represented by R^4.

Of the protecting groups, the alkyl and aralkyl groups and the groups capable of being hydrolyzed in vivo are preferred.

Examples of the substituents (a) include:
C_1 - C_6 alkyl groups, C_6 - C_{14} aryl groups, C_7 - C_{19} aralkyl groups, C_1 - C_{12} (or, as appropriate, C_1 - C_6) alkanoyl groups, C_7 - C_{15} arylcarbonyl groups, C_2 - C_7 alkoxycarbonyl groups, C_7 - C_{15} aryloxycarbonyl groups and C_8 - C_{20} aralkyloxycarbonyl groups, in all cases for example such as those exemplified above in relation to R^1 and R^2;
C_1 - C_6 haloalkyl groups, in which the alkyl part is as defined and exemplified in relation to the alkyl groups which may be represented by R^1 and R^2, and the halogen atom is chlorine, fluorine, bromine or iodine, such as the 2,2,2-trichloroethyl, 2-haloethyl (e.g. 2-chloroethyl, 2-fluoroethyl, 2-bromoethyl or 2-iodoethyl), 2,2-dibromoethyl and 2,2,2-tribromoethyl group;
halogen atoms, such as chlorine, fluorine, bromine or iodine; and
C_1 - C_6 alkoxy groups, C_6 - C_{14} aryloxy groups, C_1 - C_{12} alkanoyloxy groups, C_7 - C_{15} arylcarbonyloxy groups, C_2 - C_7 alkoxycarbonyloxy groups, C_7 - C_{15} aryloxycarbonyloxy groups and C_8 - C_{20} aralkyloxycarbonyloxy groups, respectively having a C_1 - C_6 alkyl, C_6 - C_{14} aryl, C_1 - C_{12} alkanoyl, C_7 - C_{15} arylcarbonyl, C_2 - C_7 alkoxycarbonyl, C_7 - C_{15} aryloxycarbonyl or C_8 - C_{20} aralkyloxycarbonyl portion for example such as those exemplified above in relation to R^1 and R^2;
and these examples also apply, when appropriate, to the groups R^{10}, R^{11}, R^{12} and R^{13}.

The preferred substituents (a) are C_1 - C_6 alkyl groups, trifluoromethyl groups, C_6 - C_{10} aryl groups, C_7 - C_{12} aralkyl groups, C_1 - C_6 alkanoyl groups, C_7 - C_{11} arylcarbonyl groups, C_2 - C_7 alkoxycarbonyl groups, carbamoyl groups, mono- or di-C_2 - C_7 alkylcarbamoyl groups, mono- or di-C_7 - C_{11} arylcarbamoyl groups, thiocarbamoyl groups, mono- or di- C_2 - C_7 alkylthiocarbamoyl groups, mono-or di- C_7 - C_{11} arylthiocarbamoyl groups, mono- or di-C_1 - C_6 alkylamino groups, mono- or di- phenylamino groups, mono- C_1 - C_6 alkanoylamino groups, monobenzoylamino groups, halogen atoms, nitro groups, cyano groups, hydroxy groups, C_1 - C_6 alkoxy groups, phenoxy groups, C_1 - C_6 alkanoyloxy groups, C_2 - C_7 alkoxycarbonyloxy groups, benzoyloxy groups and carboxy groups. More preferred are C_1 - C_6 alkyl groups, trifluoromethyl groups, phenyl groups, halogen atoms and C_1 - C_6 alkoxy groups; and C_1 - C_4 alkyl groups, C_1 - C_4 alkoxy groups, halogen atoms and trifluoromethyl groups are most preferred.

Examples of the substituents (b) include C_1 - C_6 alkyl groups, halogen atoms, C_6 - C_{14} aryl groups, C_7 - C_{19} aralkyl groups, C_1 - C_6 alkanoyl groups and C_7 - C_{15} arylcarbonyl groups, in all cases for example such as those exemplified above in relation to R^1 and R^2, of which C_1 - C_4 alkyl groups, phenyl groups, benzyl groups, C_1 - C_6 alkanoyl groups and benzoyl groups are preferred.

Examples of the substituents (c) include:
C_1 - C_4 alkyl, C_6 - C_{10} aryl, C_6 - C_{10} aryloxy and C_1 - C_6 alkanoyloxy groups, for example such as those exemplified above in relation to R^1 and R^2 or substituents (a):
C_1 - C_4 alkoxy groups, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy and sec-butoxy groups; and
halogen atoms, such as chlorine, fluorine, bromine or iodine.

The preferred substituents (c) are C_1 - C_4 alkyl groups, C_1 - C_4 alkoxy groups, halogen atoms, trifluoromethyl groups and nitro groups.

A preferred class of compounds of the present invention are those compounds of formula (I), in which:

R^1 and R^2 are the same or different and each represents:
a hydrogen atom,
a $C_1 - C_8$ alkyl group,
a $C_3 - C_6$ alkenyl group,
a $C_3 - C_8$ cycloalkyl group,
a $C_6 - C_{14}$ aryl group,
a substituted $C_6 - C_{14}$ aryl group having at least one of substituents (a^1) defined below,
an aralkyl or substituted aralkyl group with from 1 to 3 aryl parts each of which is $C_6 - C_{10}$ and an alkyl part which is $C_1 - C_3$, and said substituted aralkyl groups having at least one of substituents (a^1) defined below,
a $C_1 - C_6$ alkanoyl group,
a benzoyl group,
a substituted benzoyl group having at least one of substituents (a^1) defined below,
a $C_2 - C_7$ alkoxycarbonyl group,
a group of formula $-CONR^{6'}R^{7'}$,
a group of formula $-CSNR^{6'}R^{7'}$,
a benzenesulphonyl group, or
a toluenesulphonyl group,
or R^1 and R^2, together with the nitrogen atom to which they are attached, form a nitrogen-containing heterocyclic group having from 5 to 6 ring atoms, of which 0 or 1 are additional nitrogen and/or oxygen and/or sulphur hetero-atoms, said heterocyclic group being unsubstituted or having at least one of substituents (b^1) defined below, or form such a heterocyclic group fused to at least one benzene ring system which ring system is unsubstituted or has at least one of substituents (c^1) defined below;
one of R^a and R^b represents a hydrogen atom, and the other of R^a and R^b represents a group of formula (II), defined above;
R^4 represents a hydrogen atom, a $C_2 - C_5$ alkoxycarbonyl group or a benzyloxycarbonyl group;
R^5 represents a hydrogen atom, a carboxymethyl group or a protected carboxymethyl group, in which the protecting group is a $C_1 - C_4$ alkyl group, a benzyl group or a group capable of being hydrolyzed <u>in vivo</u>;
<u>n</u> = 0 or 1;
<u>X</u> represents a sulphur atom;
$R^{6'}$ and $R^{7'}$ are the same or different and each represents:
a hydrogen atom,
a $C_1 - C_6$ alkyl group,
a $C_3 - C_6$ alkenyl group,
a $C_3 - C_8$ cycloalkyl group,
a $C_6 - C_{14}$ aryl group,
a substituted $C_6 - C_{14}$ aryl group having at least one of substituents (c^1) defined below,
a benzyl group,
a benzenesulphonyl group,
a toluenesulphonyl group,
a $C_2 - C_6$ alkanoyl group, or
a $C_7 - C_{11}$ arylcarbonyl group,

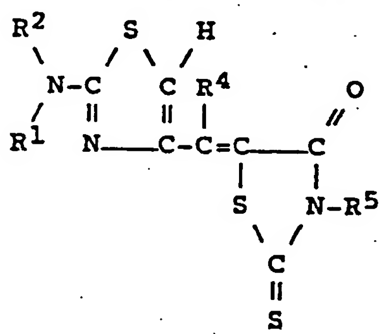
<u>substituents (a^1) :</u>
$C_1 - C_6$ alkyl groups,
trifluoromethyl groups,
$C_6 - C_{10}$ aryl groups,
$C_7 - C_{12}$ aralkyl groups,
$C_1 - C_6$ alkanoyl groups,
$C_7 - C_{11}$ arylcarbonyl groups,
$C_2 - C_7$ alkoxycarbonyl groups,
groups of formula $-CONR^{10'}R^{11'}$,
groups of formula $-CSNR^{10'}R^{11'}$,
(where $R^{10'}$ and $R^{11'}$ are the same or different and each represents a hydrogen atom, a $C_1 - C_6$ alkyl group or a $C_6 - C_{10}$ aryl group),
groups of formula $-NR^{12'}R^{13'}$,
(where $R^{12'}$ and $R^{13'}$ are the same or different and each represents a hydrogen atom, a $C_1 - C_6$ alkyl group, a phenyl group, a $C_1 - C_6$ alkanoyl group or a benzoyl group),
halogen aroms,
nitro groups,
cyano groups,
hydroxy groups,
$C_1 - C_6$ alkoxy groups,
phenoxy groups,
$C_1 - C_6$ alkanoyloxy groups,
benzoyloxy groups,

C_2 - C_7 alkoxycarbonyloxy groups, and
carboxy groups;

substituents (b^1):
oxygen atoms (i.e. to form an oxo group),
C_1 - C_4 alkyl groups,
phenyl groups,
benzyl groups,
C_1 - C_6 alkanoyl groups, and
benzoyl groups;

substituents (c^1):
C_1 - C_4 alkyl groups,
C_1 - C_4 alkoxy groups,
halogen atoms,
trifluoromethyl groups, and
nitro groups;
provided that, when R^1 represents said alkanoyl, benzoyl substituted benzoyl, alkoxycarbonyl, benzenesulphonyl or toluenesulphonyl group or said group of formula $-CONR^{6'}R^{7'}$ or $-CSNR^{6'}R^{7'}$, then R^2 represents said hydrogen atom, or said alkyl, alkenyl, cycloalkyl, aryl, substituted aryl, aralkyl or substituted aralkyl group; and pharmaceutically acceptable salts and esters thereof.

More preferred compounds of the present invention are those compounds of formula (Ia):



(Ia)

in which:
R^1 and R^2 are the same or different and each represents:
a hydrogen atom,
a C_1 - C_6 alkyl group,
a C_3 - C_6 alkenyl group,
a C_3 - C_6 cycloalkyl group,
a phenyl group,
a naphthyl group,
a substituted phenyl group or a substituted naphthyl group having at least one of substituents (a^2) defined below,
a C_7 - C_{19} aralkyl group,
a substituted C_7 - C_{19} aralkyl group having at least one of substituents (a^2) defined below,
a C_2 - C_6 alkanoyl group,
a benzoyl group,
a substituted benzoyl group having at least one of substituents (a^2) defined below,
a group of formula $-CONR^{6''}R^{7''}$, or
a group of formula $-CSNR^{6''}R^{7''}$,
or R^1 and R^2, together with the nitrogen atom to which they are attached, form a 1-pyrrolidinyl, piperidino, hexamethyleneimino, morpholino, thiomorpholino or 1-piperazinyl group which is unsubstituted or has at least one of substituents (b^2) defined below;
R^4 represents a hydrogen atom or a C_2 - C_5 alkoxycarbonyl group;
R^5 represents a hydrogen atom, a carboxymethyl group or a protected carboxymethyl group, in which the protecting group is preferably a C_1 - C_4 alkyl group, a benzyl group or the groups capable of being hydrolyzed in vivo;
$R^{6''}$ and $R^{7''}$ are the same or different and each represents:
a hydrogen atom,
a C_1 - C_6 alkyl group,
an allyl group,
a cyclohexyl group

a C_6 - C_{10} aryl group
a substituted C_6 - C_{10} aryl group having at least one of substituents (c^2) defined below,
a benzenesulphonyl group,
a toluenesulphonyl group, or
a benzoyl group,

substituents (a^2):
C_1 - C_6 alkyl groups,
trifluoromethyl groups,
phenyl groups,
halogen atoms, and
C_1 - C_6 alkoxy groups;

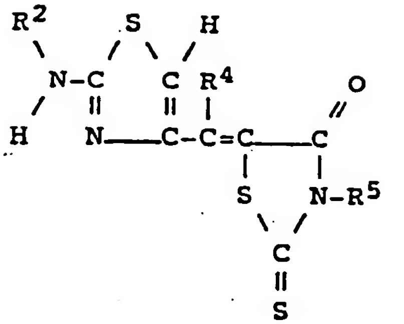
substituents (b^2):
C_1 - C_4 alkyl groups,
phenyl groups,
benzyl groups,
C_1 - C_6 alkanoyl groups, and
benzoyl groups;

substituents (c^2):
C_1 - C_4 alkyl groups,
C_1 - C_4 alkoxy groups,
halogen atoms,
nitro groups, and
trifluoromethyl groups;

provided that, when R^1 represents a hydrogen atom, R^2 represents the said groups other than a hydrogen atom, and when R^1 represents said alkanoyl, benzoyl or substituted benzoyl group or said group of formula $-CONR^{6''}R^{7''}$ or $-CSNR^{6''}R^{7''}$, then R^2 represents said hydrogen atom or said alkyl, alkenyl, cycloalkyl, phenyl, naphthyl, substituted phenyl, substituted naphthyl, aralkyl or substituted aralkyl group;
and pharmaceutically acceptable salts and esters thereof.

Still more preferred compounds of the present invention are those compounds of formula (Ia), defined above, in which:
R^1 and R^2 are the same or different and each represents:
a hydrogen atom,
a C_1 - C_4 alkyl group,
a C_3 - C_6 alkenyl group,
a C_3 - C_6 cycloalkyl group,
a phenyl group,
a substituted phenyl group having at least one C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen or trifluoromethyl substituent,
a monoarylcarbamoyl or monoaryl(thiocarbamoyl) group in which the aryl group is a C_6 - C_{10} carbocyclic aryl group which is unsubstituted or has at least one C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen, trifluoromethyl or nitro substituent,
R^4 represents a hydrogen atom or a C_2 - C_5 alkoxycarbonyl group;
R^5 represents a hydrogen atom, a carboxymethyl group or a protected carboxymethyl group, in which the protecting group is preferably a C_1 - C_4 alkyl group, a benzyl group or one of the groups capable of being hydrolyzed in vivo;
provided that, when R^1 represents a hydrogen atom, R^2 represents the said groups other than a hydrogen atom, and when R^1 represents said monoarylcarbamoyl or monoarylthiocarbamoyl group, R^2 represents said hydrogen atom or said alkyl, alkenyl, phenyl or substituted phenyl group;
and pharmaceutically acceptable salts and esters thereof.

The most preferred compounds of the present invention are those compounds of formula (Ib):



(Ib).

in which:

R^2 represents a C_1 - C_4 alkyl group, a C_3 - C_6 alkenyl group, a phenyl group, a substituted phenyl group having at least one C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen or trifluoromethyl substituent, a phenylcarbamoyl group or a phenyl(thiocarbamoyl) group in which the phenyl group is unsubstituted or has at least one C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen, trifluoromethyl or nitro substituent,

R^4 represents a hydrogen atom or a C_2 - C_5 alkoxycarbonyl group;

R^5 represents a carboxymethyl group;

and pharmaceutically acceptable salts and esters thereof.

In the compounds of the present invention, from 1 to 3 double bonds are present between the thiazole ring and the thiazolidine or rhodanine ring; and the compounds of the present invention can, therefore, form various stereoisomers. These individual stereoisomers, as well as mixtures thereof, all form part of the present invention. Furthermore, when R^5 represents a hydrogen atom in the compound of formula (I), tautomerism occurs between the nitrogen atom and the adjacent carbonyl group, and such tautomers are also included in the present invention.

The compounds of the invention may contain one or more carboxy groups and can, therefore, form salts which may, where the compounds are intended for therapeutic use, be pharmaceutically acceptable salts. Examples of such salts include:

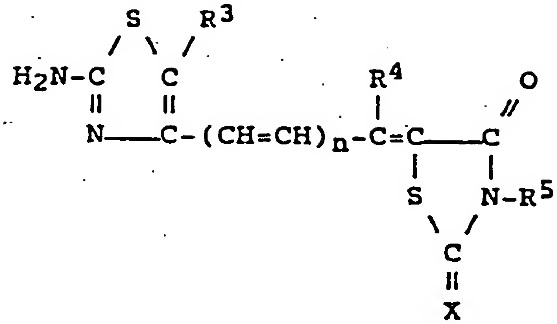
salts with alkali or alkaline earth metals, such as the sodium potassium, magnesium or calcium salts;
salts with other metals, such as the aluminium, iron and cobalt salts;
the ammonium salts;
quaternary ammonium salts, for example the tetramethylammonium, tetraethylammonium, benzyltriethylammonium and phenyltriethylammonium salts;
salts with alkylamines, cycloalkylamines or aralkylamines, such as the methylamine, methylamine, dimethylamine, diethylamine, trimethylamine, triethylamine, N-methylhexylamine, cyclopentylamine, dicyclohexylamine, benzylamine, dibenzylamine, α-phenylethylamine and ethylenediamine salts;
salts with heterocyclic amines, wherein the heterocyclic group is unsubstituted or has at least one C_1 - C_4 alkyl substituent, for example the piperidine, morpholine, pyrrolidine, piperazine, pyridine, 1-methylpiperazine and 4-ethylmorpholine salts; and
salts with amines containing a hydrophilic group, such as the monoethanolamine, ethyldiethanolamine and 2-amino-1-butanol salts.

The compounds of the present invention may also be basic in character as they necessarily contain several nitrogen atoms; they may, therefore, also form acid addition salts with suitable acids. Examples of acids include: hydrochloric acid, sulphuric acid, nitric acid and phosphoric acid; and organic carboxylic and sulphonic acids, such as acetic acid, succinic acid, maleic acid, fumaric acid, malic acid, glutamic acid, aspartic acid, p-toluenesulphonic acid and methanesulphonic acid.

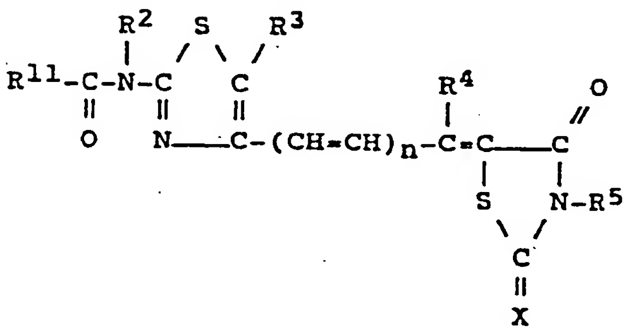
Examples of specific compounds of the invention are given in the following formulae (I-1) to (I-4), in which the substituents are as defined in the corresponding one of Tables 1 to 4 [i.e. Table 1 relates to formula (I-1). Table 2 relates to formula (I-2) and so on]. Formula (I-4) also relates to the compounds listed in Table 5, where R^1 and R^2 together form the group shown in the column headed R^1-R^2. In the Tables, the following abbreviations are used:

Ac	acetyl
All	allyl
Ant	anthryl
Boz	benzoyl
Bu	butyl
cBu	cyclobutyl
iBu	isobutyl
tBu	t-butyl
Buc	butoxycarbonyl
iBuc	isobutoxycarbonyl
tBuc	t-butoxycarbonyl
Bz	benzyl

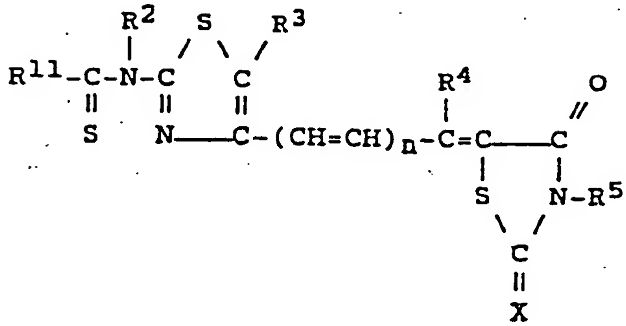
Bzc	benzyloxycarbonyl
Bzhy	benzhydryl
Bzs	benzenesulphonyl
Cam	carboxymethyl
Car	carbamoyl
Et	ethyl
Etc	ethoxycarbonyl
Hx	hexyl
_c_Hx	cyclohexyl
Me	methyl
Mec	methoxycarbonyl
Mes	methanesulphonyl
Np	naphthyl
Npc	naphthyloxycarbonyl
Oc	octyl
Ph	phenyl
Phc	phenoxycarbonyl -
Phy	phenylene, e.g. 1,2-Phy = 1,2-phenylene
Piv	pivaloyl
_c_Pn	cyclopentyl
_n_Pn	neopentyl
Pr	propyl
_c_Pr	cyclopropyl
_i_Pr	isopropyl
Prc	propoxycarbonyl
_i_Prc	isopropoxycarbonyl
_i_Pre	isopropenyl
Prg	propargyl (= 2-propynyl)
Sam	sulphamoyl
Sty	styryl
Tfm	trifluoromethyl
Tol	tolyl
Tos	_p_-toluenesulphonyl
Vin	vinyl



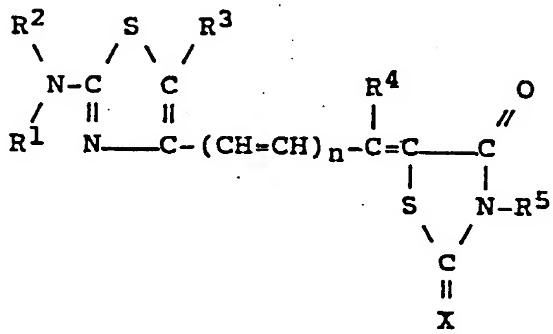
(I-1)



(I-2)



(I-3)



(I-4)

TABLE 1

Cpd. No.	R^3	R^4	R^5	n	X
1-1	H	H	H	0	O
1-2	H	H	H	0	S
1-3	H	H	Cam	0	O
1-4	H	H	Cam	0	S
1-5	H	H	Cam	1	S
1-6	H	H	(tBuc)Me	0	O
1-7	H	Etc	Cam	0	S
1-8	H	-COOH	Cam	0	S
1-9	H	iPrc	(tBuc)Me	0	S
1-10	H	Mec	Cam	0	S
1-11	H	diiPrCar	Cam	0	S
1-12	H	Etc	(Bzc)Me	0	S

TABLE 2

Cpd. No.	R^{11}	R^2	R^3	R^4	R^5	n	X
2-1	Me	H	H	Etc	Cam	0	S
2-2	tBu	H	H	iBuc	Cam	0	S
2-3	cPn	H	H	H	Cam	1	O
2-4	cHx	H	H	Etc	Cam	0	S
2-5	cHx	Ph	H	H	Cam	0	S
2-6	Vin	H	H	Etc	Cam	1	O
2-7	iPre	cHx	H	EtCar	Cam	0	S
2-8	Sty	H	H	Etc	Cam	0	S
2-9	Sty	H	H	H	Cam	0	O
2-10	Sty	H	H	Car	H	0	S
2-11	Me	H	H	Etc	Cam	0	O
2-12	Ph	H	H	Etc	Cam	0	S
2-13	Ph	H	H	Car	H	0	S
2-14	Ph	Ph	H	Etc	H	0	S
2-15	Ph	H	H	H	Cam	1	O
2-16	Ph	H	H	H	H	0	O
2-17	Ph	H	H	Car	Cam	0	O
2-18	2-Np	H	H	Etc	Cam	0	S
2-19	1-Np	Pr	H	diEtCar	Cam	0	S
2-20	9-Ant	H	H	Car	Cam	0	S
2-21	4-CℓPh	H	H	Etc	Cam	0	S
2-22	4-BrPh	H	H	H	Cam	0	O
2-23	2-HOOCPh	Et	H	H	Cam	0	S
2-24	3,5-diBrPh	H	H	Etc	Cam	0	S
2-25	2,5-diCℓPh	H	H	Etc	Cam	0	S
2-26	3,4-diCℓPh	H	H	H	Cam	0	O
2-27	pentaFPh	H	H	H	H	0	S
2-28	4-PhOPh	H	H	Etc	Cam	0	S

TABLE 2 (cont)

Cpd. No.	R^{11}	R^2	R^3	R^4	R^5	n	X
2-29	-NHPh	H	H	Etc	Cam	0	S
2-30	-NHPh	H	H	Etc	H	0	S
2-31	-NHPh	H	H	-COOH	H	0	S
2-32	-NHPh	H	H	Phc	Cam	0	S
2-33	-NHPh	H	H	Car	Cam	0	S
2-34	-N(Me)Ph	H	H	BuCar	H	0	O
2-35	$-NPh_2$	H	H	Etc	Cam	0	S
2-36	$-NPh_2$	H	H	H	Cam	1	O
2-37	$-NPh_2$	H	H	H	H	0	O
2-38	-N(All)Ph	H	H	EtCar	Cam	0	S
2-39	-NHPh	H	H	H	H	0	S
2-40	-NHPh	H	H	H	H	0	O
2-41	-NHPh	H	H	H	Cam	0	S
2-42	-NHPh	H	H	H	Cam	0	O
2-43	-NHPh	H	H	H	H	1	S
2-44	-NHPh	H	H	H	H	1	O
2-45	-NHPh	H	H	H	Cam	1	S
2-46	-NHPh	H	H	Etc	H	1	S
2-47	-NH-1-Np	H	H	Etc	Cam	0	S
2-48	-NH-1-Np	H	H	-COOH	H	0	S
2-49	-NH-1-Np	H	H	iPrc	Cam	1	S
2-50	-NH-1-Np	H	H	Car	Cam	0	O
2-51	-NH-1-Np	H	H	BuCar	(1-PivOEtc)Me	0	S
2-52	-N(1-Np)cHx	H	H	Etc	Cam	0	S
2-53	-N(1-Np)All	H	H	Car	Cam	0	S
2-54	-N(1-Np)Hx	H	H	MeCar	H	0	S
2-55	-NHPh	H	H	iBuc	Cam	0	S
2-56	-NHPh	H	H	-COOH	Cam	0	S

TABLE 2 (cont)

Cpd. No.	R^{11}	R^2	R^3	R^4	R^5	n	X
2-57	-NHPh	H	H	Etc	(1-iPrcOEtc)Me	0	S
2-58	-NHPh	H	H	Etc	(Etc)Me	0	S
2-59	-NHPh	H	H	Etc	(NaOOC)Me	0	S
2-60	-NHPh	H	H	Etc	(Mec)Me	0	S
2-61	-NHPh	H	H	Etc	(iPrc)Me	0	S
2-62	-NHPh	H	H	H	(Buc)Me	0	S
2-63	-NHPh	H	H	Etc	(Bzc)Me	0	S
2-64	p-TosNH-	H	H	Etc	Cam	0	S
2-65	p-TosNH-	H	H	Car	Cam	0	S
2-66	p-TosNH-	H	H	H	H	1	O
2-67	-NHMe	iBu	H	MeCar	Cam	0	S
2-68	$-NEt_2$	H	H	H	H	0	S
2-69	-NHtBu	H	H	Prc	Cam	0	S
2-70	-NHHx	H	H	Etc	H	0	O
2-71	-NHBz	H	H	Etc	Cam	0	S
2-72	-NH(4-CℓPh)	H	H	Etc	Cam	0	S
2-73	-NH(4-CℓPh)	H	H	iBuc	Cam	1	S
2-74	-NH(3,4--diCℓPh)	H	H	Etc	Cam	0	S
2-75	-NH(4-BrPh)	H	H	Etc	Cam	0	S
2-76	-NH(4-FPh)	H	H	Etc	Cam	0	S
2-77	-NH(3,5-diCℓ--4-HOPh)	H	H	Etc	Cam	0	S
2-78	-NH(3-CNPh)	Hx	H	Car	Cam	0	O
2-79	-NH(4-PhOPh)	H	H	Etc	Cam	0	S
2-80	-NH(3,4,5-tri--MeOPh)	H	H	Etc	Cam	0	S
2-81	-NH(3,5-ditBu--4-HOPh)	H	H	Car	Cam	0	S

TABLE 2 (cont)

Cpd. No.	R^{11}	R^2	R^3	R^4	R^5	n	X
2-82	-NH(3-FPh)	H	H	Etc	Cam	0	S
2-83	-NH(2-FPh)	H	H	Etc	Cam	0	S
2-84	-NH(4-FPh)	H	H	iBuc	Cam	0	S
2-85	-NH(4-MeOPh)	H	H	Etc	Cam	0	S
2-86	-NH(3-MeOPh)	H	H	Etc	Cam	0	S
2-87	-NH(2-MeOPh)	H	H	Etc	Cam	0	S
2-88	-NH(4-F-3-NO_2Ph)	H	H	Etc	Cam	0	S
2-89	-NH(4-TfmPh)	H	H	Etc	Cam	0	S
2-90	-NH(2,4-diFPh)	H	H	Etc	Cam	0	S
2-91	-NH(4-FPh)	H	H	Etc	Cam	1	S
2-92	-NH(2,4,6-triFPh)	H	H	Etc	Cam	0	S
2-93	-NH(4-NO_2Ph)	H	H	Etc	Cam	0	S
2-94	-NH(2-TfmPh)	H	H	Etc	Cam	0	S
2-95	-NHcHx	H	H	Etc	Cam	0	S
2-96	-NHMe	H	H	Etc	Cam	0	S
2-97	-NH(2,6-diMePh)	H	H	Etc	Cam	0	S
2-98	-NH(2-CℓPh)	H	H	Etc	Cam	0	S
2-99	-NH(4-BrPh)	H	H	H	Cam	1	S
2-100	-NH(4-FPh)	H	H	Etc	(NaOOC)Me	0	S
2-101	-NH(2-FPh)	H	H	(E)Etc	(Etc)Me	0	S
2-102	-NH(2-FPh)	H	H	(Z)Etc	(Etc)Me	0	S
2-103	-NH(4-FPh)	H	H	(E)Etc	(Etc)Me	0	S
2-104	-NH(4-FPh)	H	H	(Z)Etc	(Etc)Me	0	S
2-105	-NH(4-MePh)	H	H	Etc	Cam	0	S
2-106	$-NH_2$	H	H	Etc	Cam	0	S
2-107	$-NH_2$	H	H	H	Cam	0	S
2-108	-NHBoz	H	H	Etc	Cam	0	S
2-109	-NHBoz	H	H	H	Cam	0	S

TABLE 3

Cpd. No.	R^{11}	R^2	R^3	R^4	R^5	n	X
3-1	-NHPh	H	H	Etc	Cam	0	S
3-2	-NHPh	H	H	iBuc	Cam	1	O
3-3	-NHPh	H	H	-COOH	H	0	S
3-4	-N(Me)Ph	iPr	H	H	Cam	0	S
3-5	-N(Me)Ph	Et	H	Mec	H	0	O
3-6	-N(1-Np)Ph	H	H	Car	Cam	0	S
3-7	-NH-1-Np	H	H	Etc	Cam	0	S
3-8	-N(1-Np)Me	H	H	Etc	Cam	0	S
3-9	-NH-1-Np	H	H	Car	Cam	1	S
3-10	-NH(4-ClPh)	H	H	Etc	Cam	0	S
3-11	-NH(4-ClPh)	H	H	Car	Cam	0	S
3-12	-NH(4-ClPh)	Me	H	H	Cam	1	O
3-13	-NH(4-MeOPh)	H	H	EtCar	H	0	O
3-14	-NH(4-PhPh)	Et	H	H	Cam	0	S
3-15	-NH(4-iPrPh)	H	H	H	Cam	0	S
3-16	-NH(3-AcOPh)	H	H	H	Cam	0	S
3-17	-NH(4-FPh)	H	H	Etc	Cam	0	S
3-18	-NH(4-CNPh)	nPn	H	Car	Cam	0	O
3-19	-NH(4-EtOPh)	Pr	H	Etc	H	0	S
3-20	-NH(2-NO_2Ph)	Hx	H	Etc	Cam	0	S
3-21	-NH(2-FPh)	H	H	Etc	Cam	0	S
3-22	-NH(2-TfmPh)	H	H	Etc	Cam	0	S
3-23	-NH(2,4,6-triFPh)	H	H	Etc	Cam	0	S
3-24	-NHPh	H	H	Etc	(Etc)Me	0	S
3-25	-NH(4-ClPh)	H	H	Etc	(Etc)Me	0	S
3-26	-NHBoz	H	H	Etc	Cam	0	S
3-27	-NHBoz	H	H	H	Cam	0	S
3-28	-NH_2	H	H	Etc	Cam	0	S
3-29	-NH_2	H	H	H	Cam	0	S
3-30	-NHBoz	H	H	-COOH	Cam	0	S

TABLE 4

Cpd. No.	R^1	R^2	R^3	R^4	R^5	n	X
4-1	Ph	H	H	Etc	Cam	0	S
4-2	4-CℓPh	H	H	Etc	Cam	0	S
4-3	4-BrPh	H	H	Etc	Cam	0	S
4-4	4-FPh	H	H	Etc	Cam	0	S
4-5	4-CNPh	Ph	H	H	H	1	O
4-6	2-MeOPh	H	H	Etc	Cam	1	S
4-7	3-EtPh	Et	H	iBuc	Cam	1	S
4-8	2,4-diCℓPh	H	H	Etc	Cam	0	S
4-9	3,5-diBr-2-HOPh	H	H	H	Cam	1	S
4-10	3,5-ditBu-2-HOPh	H	H	H	H	0	S
4-11	4-CarPh	iPr	H	H	Cam	0	S
4-12	4-(BozNH)Ph	Hx	H	H	H	1	O
4-13	4-PhPh	H	H	Etc	Cam	0	S
4-14	1-Np	H	H	Car	Cam	0	O
4-15	Bz	H	H	Etc	Cam	0	S
4-16	$-CPh_3$	H	H	H	H	0	S
4-17	$-CPh_3$	H	H	H	H	0	O
4-18	$-CPh_3$	H	H	H	Cam	0	S
4-19	$-CPh_3$	H	H	H	Cam	0	O
4-20	$-CPh_3$	H	H	H	H	1	S
4-21	$-CPh_3$	H	H	H	H	1	O
4-22	$-CPh_3$	H	H	H	Cam	1	S
4-23	$-CPh_3$	H	H	H	Cam	1	O
4-24	$-CPh_3$	H	H	-COOH	Cam	1	S
4-25	$-CPh_3$	H	H	-COOH	Cam	1	O
4-26	$-CPh_3$	H	H	Etc	Cam	1	S
4-27	$-CPh_3$	H	H	Etc	Cam	1	O
4-28	Bz	Me	H	Etc	Cam	0	S
4-29	Bz	Ph	H	H	Cam	1	S

TABLE 4 (cont)

Cpd. No.	R^1	R^2	R^3	R^4	R^5	n	X
4-30	$-CPh_3$	H	H	H	(tBuc)Me	0	O
4-31	Ph	H	H	H	Cam	0	S
4-32	Ph	H	H	H	(Etc)Me	0	S
4-33	Ph	H	H	H	(1-iPrcOEtc)Me	0	S
4-34	Ph	H	H	H	Cam	1	S
4-35	Ph	H	H	H	(NaOOC)Me	0	S
4-36	Ph	H	H	Etc	Cam	0	S
4-37	4-FPh	H	H	H	Cam	0	S
4-38	4-FPh	H	H	H	(NaOOC)Me	0	S
4-39	4-FPh	H	H	H	(Etc)Me	0	S
4-40	4-FPh	Et	H	H	Cam	0	S
4-41	3-FPh	H	H	H	Cam	0	S
4-42	2-FPh	H	H	H	Cam	0	S
4-43	Ph	Me	H	H	Cam	0	S
4-44	2,4-diFPh	H	H	H	Cam	0	S
4-45	2,4-diFPh	H	H	H	(1-iPrcOEtc)Me	0	S
4-46	2,4,6-triFPh	H	H	H	Cam	0	S
4-47	2,4,5-triFPh	H	H	H	Cam	0	S
4-48	2-Cl-4-FPh	H	H	H	Cam	0	S
4-49	4-F-2-TfmPh	H	H	H	(NaOOC)Me	0	S
4-50	2-Br-4,6-diFPh	H	H	H	Cam	1	S
4-51	2-EtO-4-F-$-6-NO_2Ph$	H	H	H	(Etc)Me	0	S
4-52	4-Cl-2-FPh	H	H	H	(Buc)Me	0	S
4-53	4-TfmPh	H	H	H	Cam	0	S
4-54	4-TfmPh	H	H	H	(NaOOC)Me	0	S
4-55	4-TfmPh	H	H	H	(Etc)Me	0	S
4-56	4-TfmPh	H	H	H	(1-iPrcOEtc)Me	0	S

TABLE 4 (cont)

Cpd. No.	R^1	R^2	R^3	R^4	R^5	n	X
4-57	3-TfmPh	H	H	H	Cam	0	S
4-58	2-TfmPh	H	H	H	Cam	0	S
4-59	2-AcNH-5-TfmPh	H	H	H	Cam	0	S
4-60	$2\text{-}NO_2\text{-}4\text{-}TfmPh$	H	H	H	Cam	0	S
4-61	1-Np	H	H	H	Cam	0	S
4-62	2-Np	H	H	H	Cam	0	S
4-63	4-F-1-Np	H	H	H	Cam	0	S
4-64	4-CℓPh	H	H	H	Cam	0	S
4-65	3-CℓPh	H	H	H	Cam	0	S
4-66	2-CℓPh	H	H	H	Cam	0	S
4-67	4-BrPh	H	H	H	Cam	0	S
4-68	$3\text{-}NO_2Ph$	H	H	H	Cam	0	S
4-69	p-Tol	H	H	H	Cam	0	S
4-70	m-Tol	H	H	H	Cam	0	S
4-71	o-Tol	H	H	H	Cam	0	S
4-72	4-iPrPh	H	H	H	Cam	0	S
4-73	4-MeOPh	H	H	H	Cam	0	S
4-74	3-MeOPh	H	H	H	Cam	0	S
4-75	2-MeOPh	H	H	H	Cam	0	S
4-76	3-EtNHPh	H	H	H	Cam	0	S
4-77	4-PhNHPh	H	H	H	Cam	0	S
4-78	4-PhPh	H	H	H	Cam	0	S
4-79	4-PhOPh	H	H	H	Cam	0	S
4-80	$4\text{-}(NMe_2)Ph$	H	H	H	Cam	0	S
4-81	4-CNPh	H	H	H	Cam	0	S
4-82	4-EtcPh	H	H	H	Cam	0	S
4-83	2-HOOCPh	H	H	H	Cam	0	S
4-84	4-HOPh	H	H	H	Cam	0	S

TABLE 4 (cont)

Cpd. No.	R^1	R^2	R^3	R^4	R^5	n	X
4-85	3-HOPh	H	H	H	Cam	0	S
4-86	2-HOPh	H	H	H	Cam	0	S
4-87	3,5-ditBu-4-HOPh	H	H	H	Cam	0	S
4-88	4-HO-3,5-diMePh	H	H	H	Cam	0	S
4-89	4-(EtCar)Ph	H	H	H	Cam	0	S
4-90	2-SamPh	H	H	H	Cam	0	S
4-91	3-AcPh	H	H	H	Cam	0	S
4-92	4-BozPh	H	H	H	Cam	0	S
4-93	4-AcOPh	H	H	H	Cam	0	S
4-94	4-BozOPh	H	H	H	Cam	0	S
4-95	3,4,5-triMeOPh	H	H	H	Cam	0	S
4-96	Bzhy	H	H	H	Cam	0	S
4-97	Bzhy	H	H	H	(Etc)Me	0	S
4-98	Bzhy	H	H	H	(NaOOC)Me	0	S
4-99	4,4'-diFBzhy	H	H	Etc	Cam	0	S
4-100	4,4'-diFBzhy	H	H	H	Cam	0	S
4-101	di(2-Np)Me	H	H	H	Cam	0	S
4-102	(4-FPh)(2-Np)Me	H	H	H	Cam	0	S
4-103	Bz	H	H	H	Cam	0	S
4-104	Ph	Ph	H	H	Cam	0	S
4-105	Ph	Me	H	H	Cam	0	S
4-106	Phc	H	H	Etc	Cam	0	S
4-107	1-Npc	H	H	Car	Cam	0	S
4-108	Phc	Me	H	iPrc	Cam	0	S
4-109	Mec	Ph	H	Etc	Cam	0	S
4-110	Etc	Ph	H	MeCar	Cam	0	S
4-111	iPrc	H	H	-COOH	(Mec)Me	0	S
4-112	Bzc	H	H	H	H	0	S

TABLE 4 (cont)

Cpd. No.	R^1	R^2	R^3	R^4	R^5	n	X
4-113	Bzc	Me	H	Etc	Cam	0	S
4-114	Bzc	Et	H	Etc	Cam	0	S
4-115	Bzc	Ph	H	Buc	(1-PivOEtc)Me	0	S
4-116	1-Me-1-PhEtc	H	H	Etc	Cam	0	S
4-117	BzhyOCO-	H	H	Etc	Cam	0	S
4-118	Bzs	H	H	Etc	Cam	0	S
4-119	Bzs	H	H	Etc	H	0	S
4-120	Bzs	H	H	H	Cam	0	O
4-121	Mes	H	H	Etc	Cam	0	O
4-122	Mes	iBu	H	Etc	H	0	O
4-123	Tos	Hx	H	Car	Cam	0	O
4-124	Me	H	H	H	Cam	0	S
4-125	Et	H	H	H	Cam	0	S
4-126	iPr	H	H	H	Cam	0	S
4-127	Bu	H	H	H	Cam	0	S
4-128	tBu	H	H	H	Cam	0	S
4-129	Me	Me	H	Etc	Cam	0	S
4-130	Et	Me	H	H	Cam	0	S
4-131	cPn	Et	H	H	Cam	0	S
4-132	cHx	H	H	H	Cam	0	S
4-133	All	H	H	H	Cam	0	S
4-134	All	iBu	H	H	Cam	0	S
4-135	Oc	H	H	H	Cam	0	S
4-136	Et	Et	H	H	Cam	0	S
4-137	Prg	H	H	H	Cam	0	S
4-138	Prg	Me	H	H	Cam	0	S
4-139	α,α-diMePrg	H	H	H	Cam	0	S
4-140	Pr	H	H	H	Cam	0	S

TABLE 4 (cont)

Cpd. No.	R^1	R^2	R^3	R^4	R^5	n	X
4-141	cPr	H	H	H	Cam	0	S
4-142	cPr	H	H	Etc	Cam	0	S
4-143	cBu	H	H	H	Cam	0	S
4-144	cBu	H	H	Etc	Cam	0	S
4-145	cPn	H	H	H	Cam	0	S
4-146	cPn	H	H	Etc	Cam	0	S

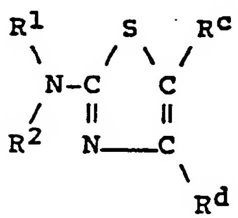
TABLE 5

Cpd. No.	R^1-R^2	R^3	R^4	R^5	n	X
5-1	$-(CH_2)_4-$	H	H	Cam	0	S
5-2	$-(CH_2)_5-$	H	Mec	Cam	0	S
5-3	$-CO(CH_2)_2CO-$	H	Etc	H	0	S
5-4	-COCH=CHCO-	H	Etc	Cam	0	S
5-5	-COCCℓ=CCℓCO-	H	Etc	Cam	0	S
5-6	-COCCℓ=CCℓCO-	H	H	Cam	0	O
5-7	-CO(1,2-Phy)CO-	H	H	Cam	0	S
5-8	-CO(1,2-Phy)CO-	H	Etc	Cam	0	S
5-9	$-(CH_2)_2-O-(CH_2)_2-$	H	H	H	0	O
5-10	$-(CH_2)_2-O-(CH_2)_2-$	H	H	Cam	0	S
5-11	$-(CH_2)_2-O-(CH_2)_2-$	H	Etc	Cam	0	S
5-12	$-(CH_2)_6-$	H	H	Cam	0	S
5-13	$-(CH_2)_2-NH-(CH_2)_2-$	H	H	Cam	0	S
5-14	$-(CH_2)_2-NMe-(CH_2)_2-$	H	H	Cam	0	S
5-15	$-(CH_2)_2-N\underline{i}Bu-(CH_2)_2-$	H	H	Cam	0	S
5-16	$-(CH_2)_2-NPh-(CH_2)_2-$	H	H	Cam	0	S
5-17	$-(CH_2)_2-NBz-(CH_2)_2-$	H	H	Cam	0	S
5-18	$-(CH_2)_2-NAc-(CH_2)_2-$	H	H	Cam	0	S
5-19	$-(CH_2)_5-$	H	H	Cam	0	S
5-20	$-(CH_2)_2-S-(CH_2)_2-$	H	H	Cam	0	S
5-21	$-(CH_2)_2-NBoz-(CH_2)_2-$	H	H	Cam	0	S
5-22	$-CH_2-S-(CH_2)_2-$	H	H	Cam	0	S

Of the compounds listed above, the following are preferred, that is to say Compounds No. 2-12, 2-29, 2-30, 2-35, 2-39, 2-41, 2-42, 2-47, 2-59, 2-72, 2-74, 2-75, 2-76, 2-80, 2-82, 2-83, 2-85, 2-86, 2-87, 2-88, 2-89, 2-90, 2-92, 2-93, 2-94, 2-96, 2-97, 2-98, 2-99, 2-105, 3-1, 3-10, 3-17, 3-21, 3-30, 4-18, 4-19, 4-31, 4-34, 4-37, 4-57, 4-73, 4-99, 4-104, 4-125, 4-126, 4-129, 4-132, 4-133, 4-136, 4-141 and 5-10, of which the following are more preferred, that is to say Compounds No. 2-29, 2-41, 2-47, 2-72, 2-76, 2-80, 2-83, 2-88, 2-90, 2-92, 2-105, 3-1, 3-10, 3-17, 3-21, 3-30, 4-18, 4-31, 4-37, 4-57, 4-73, 4-99, 4-104, 4-125, 4-126, 4-132, 4-133, 4-136, 4-141 and 5-10; and the following are most preferred, that is to say:

2-29. 5-{1-ethoxycarbonyl-1-[2-(3-phenylureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid;
2-41. 5[2-(3-phenylureido)thiazol-4-ylmethylene]rhodanine-3-acetic acid;
2-47. 5-{1-ethoxycarbonyl-1-[2-(3-naphthyl)ureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid;
2-72. 5-{1-[2-(3-p-chlorophenylureido)thiazol-4-yl]-1-ethoxycarbonylmethylene}rhodanine-3-acetic acid;
2-76. 5-{1-[2-(3-p-fluorophenylureido)thiazol-4-yl]-1-ethoxycarbonylmethylene}rhodanine-3-acetic acid;
2-88. 5-{1-ethoxycarbonyl-1-[2-[3-(4-fluoro-3-nitrophenyl)ureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid;
2-92. 5-{1-ethoxycarbonyl-1-[2-[3-(2,4,6-trifluorophenyl)ureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid;
3-1. 5-{1-ethoxycarbonyl-1-[2-(3-phenylthioureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid;
3-10. 5-{1-[2-(3-p-chlorophenylthioureido)thiazol-4-yl]-1-ethoxycarbonylmethylene}rhodanine-3-acetic acid;
4-125. 5-(2-ethylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid;
4-126. 5-(2-isopropylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid;
4-133. 5-(2-allylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid;
4-141. 5-(2-cyclopropylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid;
and pharmaceutically acceptable salts and esters thereof.

The compounds of the present invention can be prepared by a variety of methods well known for the preparation of compounds of this type. For example, they may be prepared by reacting a compound of formula (III):

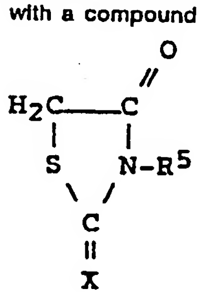


(III)

in which R^1 and R^2 are as defined above, and one of R^c and R^d represents a hydrogen atom, a C_1 - C_8 alkyl group or a halogen atom, and the other of R^c and R^d represents a group of formula (IV):

$-(CH=CH)_n-\overset{O}{\overset{\|}{C}}-R^4$ (IV)

(in which R^4 and $\underline{n}$ are as defined above)
with a compound of formula (V):



(V)

(in which R^5 and X are as defined above), and then, if required, converting any group represented by R^1, R^2, R^4 or R^5 to any other such group.

There is no particular restriction on the nature of the solvent, provided that it has no adverse effect on the reaction or on the reagents. Examples of suitable solvents include: organic carboxylic acids, such as acetic acid or trifluoroacetic acid; alcohols, such as methanol or ethanol; ethers, such as diethyl ether or tetrahydrofuran; or a mixture of any two or more thereof, or a mixture of any one or more thereof with water.

The reaction will take place over a wide range of temperatures, and the precise reaction temperature chosen is not critical to the invention. In general, we find it convenient to carry out the reaction either at room temperature, for a period of around from 1 to 5 days, or with heating (below about 100 °C) for from 5 minutes to 20 hours.

In order to accelerate the reaction, we prefer to carry it our in the presence of ammonia or an organic base, for example an amine such as methylamine, ethylamine, diethylamine, propylamine, diisopropylamine,

piperidine, pyrrolidine or morpholine, and/or a salt, such as sodium acetate, ammonium acetate or ammonium chloride.

If required, a compound of formula (I) in which R^5 represents a hydrogen atom may be converted to a corresponding compound in which R^5 represents a protected carboxyalkyl group by reacting it with a compound of formula (VI):

Z-D-CO_2E (VI)

(wherein Z represents a halogen atom, such as a chlorine atom or a bromine atom, D represents a straight or branched chain alkylene group having from 1 to 6, preferably from 1 to 3, carbon atoms, and more preferably one carbon atom; and E represents a carboxy-protecting group, e.g. as exemplified in relation to R^4).

The reaction is usually effected in a solvent (for example a ketone such as acetone or an amide such as dimethylformamide), in the presence or absence of a base (for example a carbonate such as sodium hydrogen carbonate or potassium carbonate), at a temperature from 0 to 50 °C. for a period of from 0.5 to 10 hours.

Of the compounds of formula (I), those wherein R^1 or R^2 represents a hydrogen atom can be converted to other corresponding compounds by alkylation, carbamoylation, acylation, thiocarbamoylation, sulphonylation and sulphenylation, as desired, by reaction with the corresponding halide, such as an alkyl halide, or the corresponding isocyanate or isothiocyanate, such as an arylisocyanate or arylisothiocyanate. The reaction with a halide is usually effected in a solvent (for example an ether, such as tetrahydrofuran, or an amide, such as dimethylformamide), in the presence or absence of a base (for example an organic amine such as triethylamine or pyridine), at a temperature from 0 to 50 °C, for a period of from 10 minutes to 1 day. The reaction with an isocyanate is usually effected in a solvent, for example an amide such as dimethylformamide or hexamethyl phosphoric triamide, at a temperature from room temperature to 100 °C, for a period of from 1 hour to 20 hours.

Where the compound of the present invention thus prepared contains a carboxy group or an alkoxycarbonyl group in the group represented by R^4 and/or R^5, the compound can be converted to a corresponding ester compound by an esterification reaction or an ester exchange reaction, or it may be converted to a corresponding amide compound by an amidation reaction, all of which are well known in the art and may be carried out by well known techniques. Furthermore, such esters and amides can be converted to the corresponding carboxylic acid by hydrolysis, which, again, may be carried out by well known means.

The esterification is usually carried out by reaction with a halide or alcohol corresponding to the desired ester group. The reaction with a halide is usually effected in a solvent (for example an amide such as dimethylformamide or hexamethyl phosphoric triamide), in the presence of a base (for example an organic amine, such as triethylamine or pyridine, or an alkali, such as sodium hydroxide), at a temperature of from 0 to 100 °C, for a period of from 5 hours to 3 days. The reaction with an alcohol is usually effected in a solvent (for example an ether such as tetrahydrofuran or dioxane, or an excess of the alcohol itself which is used in the reaction), in the presence of an acid (for example a mineral acid, such as hydrochloric acid, or a sulphonic acid, such as p-toluenesulphonic acid), at a temperature of from 0 to 50 °C, for a period of from 5 hours to 3 days.

At the end of any of the above-mentioned steps in the sequence of reactions for preparing the compounds of the invention, the desired compound may be isolated or purified by known separation or purification methods, such as concentration, concentration under reduced pressure, extraction with solvent crystallization and recrystallization, solvent substitution, or the various chromatography techniques, notably preparative thin layer chromatography or column chromatography.

The thiazole compound of formula (III) which contains a carbonyl group, which is used as a starting material in the process of the present invention, can be prepared by the method described in Heterocyclic Compounds, 34 (No. 1 to 3) John Wiley & Sons, New York.

A compound of formula (III) in which one of R^c and R^d represents a group of formula -CHO, that is to say an aldehyde, can be prepared by reducing a corresponding compound in which one of R^c and R^d represents a group of formula -CO-COO-alkyl or -COO-alkyl with a metal hydride, such as sodium borohydride or lithium aluminium hydride, and then oxidizing the resulting 1,2-diol with a metal salt of a metaperhalogenic acid such as sodium metaperiodide, or oxidizing the resulting primary alcohol with an oxidizing agent such as manganese dioxide or sulphur trioxide pyridine complex.

In the compounds of formula (I), when R^5 represents a hydrogen atom and/or when the compound of formula (I) contains an acidic group, such as a carboxy or sulpho group, the compound of formula (I) can be converted to a pharmaceutically acceptable non-toxic salt by conventional means. Examples of such salts have been given above; and preferred examples include: alkali metal salts, such as the sodium and potassium salts; alkaline earth metal salts, such as the calcium salt; salts of trivalent metals, such as the aluminium salt; and salts of organic bases, such as the morpholine, piperidine, lysine and arginine salts.

Those compounds having basicity may also be converted to acid addition salts by methods well known in the art to form, for example, an inorganic acid salt, such as the hydrochloride, sulphate, nitrate or phosphate; or an organic carboxylic or sulphonic acid salt, such as the acetate, succinate, maleate, fumarate, malate, glutamate, aspartate, p-toluenesulphonate or methanesulphonate.

The compounds of the invention are inhibitors of the enzyme aldose reductase, which is implicated in many of the complications of diabetes, and are therefore of value as medicaments in the treatment and prevention of such complications. For instance, this inhibitory activity is exhibited in vitro by the compounds of the invention in tests using an isolated rat or bovine ocular lens, or human erythrocytes or placental tissue. They also show notable activity in vivo in lowering the sorbitol content in the nervous tissues of a model diabetic animal. They

seem to have low toxicity and, in particular, produce very low hepatomegaly in test animals such as mice or rats.

The enzyme-inhibiting activity and low toxicity of the compounds of the invention are demonstrated in the following experiments.

Inhibition of Aldose Reductase

Human placental aldose reductase was separated and partially purified by the method of Kador et al. [Anal. Biochem., 114, 53 - 58 (1981)]; and its activity was determined photometrically by the method of Varma et al. [Biochem. Pharmac., 25, 2505 (1976)]. Inhibition of enzyme activity was measured for the seven compounds of the invention and the control compound shown in Table 6, using each test compound at a concentration of 1 x 10^{-5}M.

The results obtained are shown in Table 6, in which the seven compounds of the invention are identified by the numbers used in Tables 1 - 5 above, and also by the numbers of the corresponding Examples below which illustrate the preparation of these compounds. The control compound Compound A, is 5-(thiophen-2-ylmethylene)rhodanine-3-acetic acid, which is disclosed in European Patent Publication No. 47,109.

Table 6

Compound Number	Example Number	Percentage Inhibition
2-29	1	83.1 %
2-72	14	85.2 %
2-76	13	87.1 %
2-88	44	100.0 %
2-92	45	85.6 %
3-1	6	90.4 %
3-10	7	93.9 %
Compound A		34.4 %

Toxicity

The test animals were male mice of the ddy strain, used in six groups, each group consisting of three animals. A single test compound was administered orally to the animals in each group, at a dose of 300 mg/kg body weight. The compounds employed were those identified in Tables 1 - 5 above as Compounds Nos. 2-29, 2-72, 2-76, 2-92, 3-1 and 3-10. The animals were then observed for one week after administration, during which time they showed no abnormalities which could be attributed to the test compounds. All the animals were alive at the end of the one week observation period.

In view of the substantial dose administered to each animal, the zero mortality indicates that the compounds of the invention have a very low toxicity.

Accordingly, the compounds of the invention may be expected to be effective in the treatment of complications of human diabetes, such as diabetic cataract, diabetic neuropathy and diabetic nephropathy. Their mode of administration will depend on individual circumstances, such as the type of condition under treatment. For example, they may be administered orally, in pharmaceutical formulations such as tablets, capsules, powders, granules and the like, or parenterally in pharmaceutical formulations such as injections (intravenous, subcutaneous or intramuscular), suppositories and the like. For administration to the ocular mucosa, an ophthalmic solution or ophthalmic ointment may preferably be used. These pharmaceutical preparations can be prepared by conventional means and may contain known excipients and adjuvants of a type commonly used in this field, for example vehicles, binders, disintegrators, lubricants, correctives, etc.,

depending upon the intended use and form of the preparation. The dose of active compound will depend upon the condition, age, and body weight of the patient, as well as upon the nature and severity of the disorder to be treated; but for therapy of diabetic complications the adult daily dose, though depending on the method of administration, may be expected to be in the range of from 0.01 mg to 2 g administered orally or parenterally, and preferably from 100 mg to 1 g for oral administration.

The invention is further described with reference to the following non-limiting Examples and Preparations, which show, respectively, the synthesis of compounds in accordance with the present invention and of starting materials useful in preparing such compounds.

EXAMPLE 1

5-[1-Ethoxycarbonyl-1-[2-(3-phenylureido)thiazol-4-yl]methylene]rhodanine-3-acetic acid

A mixture comprising 1 g of ethyl 2-(3-phenylureido)thiazol-4-ylglyoxylate, 0.59 g of rhodanine-3-acetic acid, 0.4 g of ammonium chloride, 0.4 ml of 28% v/v aqueous ammonia and 4 ml of ethanol was stirred at an external temperature of 80 °C for one hour. The reaction mixture was then acidified with dilute hydrochloric acid and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulphate, and the solvent was evaporated off under reduced pressure. The residue thus obtained was purified by silica gel column chromatography, using as eluent a 50:1:1:1 by volume mixture of benzene, ethyl acetate, ethanol and acetic acid. The product thus obtained was recrystallized from acetic acid, to give 0.74 g of the desired compound as a yellow powder.

Melting point: 246 to 250 °C

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:

1.34 (3H, triplet, J = 7 Hz),
4.42 (2H, quartet, J = 7 Hz),
4.70 (2H, broad singlet),
7.07 (1H, broad triplet, J = 7 Hz),
7.35 (2H, broad triplet, J = 7 Hz),
7.49 (2H, broad doublet, J = 7 Hz),
7.70 (1H, singlet),
8.96 (1H, broad singlet),
11.02 (1H, broad singlet).

EXAMPLE 2

5-[1-Ethoxycarbonyl-1-[2-[3-(1-naphthyl)ureido]thiazol-4-yl]methylene]rhodanine-3-acetic acid

Following a procedure similar to that described in Example 1, 0.45 g of the desired compound was prepared from 3.7 g of ethyl 2-[3-(1-naphthyl)ureido]thiazol-4-yl-glyoxylate, 1.53 g of 3-rhodanineacetic acid, 1 g of ammonium chloride, 1 ml of a 28% v/v aqueous ammonia and 20 ml of ethanol. The product was a yellow powder having the following physical properties.

Melting point: 263 to 265 °C

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:

1.34 (3H, triplet, J = 7 HZ),
4.43 (2H, quartet, J = 7 Hz),
4.70 (2H, singlet),
7.49-7.76 (4H, multiplet),
7.72 (1H, singlet),
7.95-8.13 (3H, multiplet),
9.15 (1H, broad singlet),
11.36 (1H, broad singlet).

EXAMPLE 3

5-[1-(2-Acetylaminothiazol-4-yl)-1-ethoxycarbonylmethylene]rhodanine-3-acetic acid 1/3 hydrate

A mixture comprising 4.35 g of ethyl 2-aminothiazol-4-ylglyoxylate, 5 g of rhodanine-3-acetic acid, 2.7 g of sodium acetate and 50 ml of acetic acid was heated under reflux for 2 days. The reaction mixture was then worked up as in Example 1, to give the desired compound as a yellow powder.
Melting point: 292 to 296 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.33 (3H, triplet, J = 7 Hz),
2.22 (3H, singlet),
4.42 (2H, quartet, J = 7 Hz),
4.68 (2H, singlet),
7.73 (1H, singlet),
12.47 (1H, broad singlet).

EXAMPLE 4

5-[1-(2-Aminothiazol-4-yl)-1-ethoxycarbonylmethylene]rhodanine-3-acetic acid monohydrate

The desired compound was prepared by reacting at room temperature, for 15 minutes, 20 g of ethyl 2-aminothiazol-4-ylglyoxylate, 22.9 g of rhodanine-3-acetic acid, 11 g of ammonium chloride, 15 ml of 28% v/v aqueous ammonia and 200 ml of ethanol, following a procedure similar to that described in Example 1. The resulting orange product had the following physical properties.
Melting point: 250 to 254 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.31 (3H, triplet, J = 7 Hz),
4.37 (2H, quartet, J = 7 Hz),
4.66 (2H, singlet),
7.20 (1H, singlet),
7.64 (2H, broad singlet).

EXAMPLE 5

5-{1-Ethoxycarbonyl-1-[2-(3-p-toluenesulphonylureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid monohydrate

Following a procedure similar to that described in Example 1, the desired compound was prepared from 4 g of ethyl 2-(3-p-toluenesulphonylureido)thiazol-4-ylglyoxylate, 2 g of rhodanine-3-acetic acid, 1 g of ammonium chloride, 1 ml of 28% v/v aqueous ammonia and 10 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 207 to 209 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.31 (3H, triplet, J = 7 Hz),
2.40 (3H, singlet),
4.40 (2H, quartet, J = 7 Hz),
4.68 (2H, singlet),
7.43 (2H, doublet, J = 8 Hz),
7.70 (1H, singlet),
7.87 (2H, doublet, J = 8 Hz),
11.32 (1H, broad singlet).

EXAMPLE 6

5-{1-Ethoxycarbonyl-1-[2-(3-phenylthioureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid

Following a procedure similar to that described in Example 1, 0.60 g of the desired compound was prepared from 3.35 g of ethyl 2-(3-phenylthioureido)thiazol-4-ylglyoxylate, 1.7 g of rhodanine-3-acetic acid, 1 g of ammonium chloride, 1 ml of 28% v/v aqueous ammonia and 30 ml of ethanol. The resulting product was a yellow powder having the following physical properties.

Melting point: 240 to 248 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J = 7 Hz),
4.42 (2H, quartet, J = 7 Hz),
4.70 (2H, singlet),
7.22 (1H, broad triplet, J = 8 Hz),
7. 41 (2H, broad triplet, J = 8 Hz),
7. 63 (2H, broad doublet, J = 8 Hz),
7. 65 (2H, singlet),
10.33 (1H, broad singlet),
11. 8-12 .2 (1H, broad singlet),
12. 9- 13. 6 (1H, broad singlet).

EXAMPLE 7

5-[1-[2-(3-p-Chlorophenylthioureido)thiazol-4-yl]-1-ethoxycarbonylmethylene]rhodanine-3-acetic acid

Following a procedure similar to that described in Example 1, 0.39 g of the desired compound was prepared from 0.93 g of ethyl 2-(3-p-chlorophenylthioureido)thiazol-4-yl-glyoxylate 0.48 g of rhodanine-3-acetic acid, 0.25 g of ammonium chloride, 0.25 ml of 28% v/v aqueous ammonia and 5 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 225 to 235 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J = 7 Hz),
4.42 (2H, quartet, J = 7 Hz),
4.70 (2H, singlet),
7.47 (2H, broad doublet),
7.65 (2H, broad doublet),
7.67 (1H, singlet),
10.38 (1H, broad singlet),
12.06 (1H, broad singlet),
13.0-13.7 (1H, broad singlet).

EXAMPLE 8

5-[1-(2-Benzamidothiazol-4-yl)-1-ethoxycarbonylmethylene]rhodanine-3-acetic acid

Following a procedure similar to that described in Example 1, the desired compound was prepared from 3.04 g of ethyl 2-benzamidothiazol-4-ylglyoxylate, 1.91 g of rhodanine-3-acetic acid, 1 g of ammonium chloride, 1 ml of 28% v/v aqueous ammonia and 20 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 278 to 281 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.35 (3H, triplet, J = 7 Hz),
4.44 (2H, quartet, J = 7 Hz),
4.70 (2H, singlet),
7.57-7.72 (3H, multiplet),
7.83 (1H, singlet),
8.12 (2H, broad doublet, J = 7 Hz),
12.91 (1H, broad singlet),
13.1-13.6 (1H, broad singlet).

EXAMPLE 9

5-[1-Ethoxycarbonyl-1-[2-(3-phenylureido)thiazol-4-yl]methylene]rhodanine acetic acid adduct

Following a procedure similar to that described in Example 1, the desired compound was prepared from 3 g of ethyl 2-(3-phenylureido)thiazol-4-ylglyoxylate, 1.25 g of rhodanine, 1 g of ammonium chloride, 1 ml of 28% v/v aqueous ammonia and 10 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: circa 257 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.32 (3H, triplet, J = 7 Hz),
1.91 (3H, singlet),
4.39 (2H, quartet, J = 7 Hz),
7.07 (1H, broad triplet, J = 7 Hz),
7.34 (2H, broad triplet, J = 7 Hz),
7.48 (2H, broad doublet, J = 7 Hz),
7.58 (1H, singlet),
8.93 (1H, broad singlet),
10.94 (1H, broad singlet),
11.7-12.2 (1H, broad singlet),
13.73 (1H, broad singlet).

EXAMPLE 10

5-[1-[2-(3-o-Methoxyphenylureido)thiazol-4-yl]-1-ethoxycarbonylmethylene]rhodanine-3-acetic acid monohydrate

Following a procedure similar to that described in Example 1, the desired compound was prepared from 1.75 g of ethyl 2-(3-o-methoxyphenylureido)thiazol-4-ylglyoxylate, 0.95 g of rhodanine-3-acetic acid, 0.5 g of ammonium chloride, 0.5 ml of 28% v/v aqueous ammonia and 25 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: circa 230 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J = 7 Hz),
3.91 (3H, singlet),
4.42 (2H, quartet, J = 7 Hz),
4.69 (2H, singlet),
6.9-7.0 (1H, multiplet),
7.0-7.1 (2H, multiplet),
7.69 (1H, singlet),
8.1-8.15 (1H, multiplet),
8.76 (1H, broad singlet, disappeared on adding deuterium oxide),
11.54 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 11

5-[1-[2-(3-m-Methoxyphenylureido)thiazol-4-yl]-1-ethoxycarbonylmethylene]rhodanine-3-acetic acid monohydrate

Following a procedure similar to that described in Example 1, the desired compound was prepared from 1.75 g of ethyl 2-(3-m-methoxyphenylureido)thiazol-4-ylglyoxylate, 0.95 g of rhodanine-3-acetic acid, 0.5 g of ammonium chloride, 0.5 ml of 28% v/v aqueous ammonia and 20 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 208 to 212 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J = 7 Hz),
3.76 (3H, singlet),
4.42 (2H, quartet, J = 7 Hz),
4.69 (2H, singlet),
6.65 (1H, doublet of doublets, J = 2 and 8 Hz),
6.98 (1H, doublet of doublets, J = 2 and 8 Hz),
7.18 (1H, triplet, J = 2 Hz),
7.24 (1H, triplet, J = 8 Hz),

7.70 (1H, singlet),
8.97 (1H, broad singlet, disappeared on adding deuterium oxide),
11.02 (1H, broad singlet, disappeared on adding deuterium oxide),
13.1-13.7 (1H, broad, disappeared on adding deuterium oxide).

EXAMPLE 12

5-{1-[2-(3-p-Methoxyphenylureido)thiazol-4-yl]-1-ethoxycarbonylmethylene}rhodanine-3-acetic acid

Following a procedure similar to that described in Example 1, the desired compound was prepared from 1.75 g of ethyl 2-(3-p-methoxyphenylureido)thiazol-4-ylglyoxylate, 0.95 g of rhodanine-3-acetic acid, 0.5 g of ammonium chloride, 0.5 ml of 28% v/v aqueous ammonia and 20 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 230 to 235 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.33 (3H, triplet, J = 7 Hz),
3.74 (3H, singlet),
4.41 (2H, quartet, J = 7 Hz),
4.69 (2H, singlet),
6.91 (2H, doublet, J = 9 Hz),
7.39 (2H, doublet, J = 9 Hz),
7. 67 (1H, singlet),
8.79 (1H, broad singlet),
10.99 (1H, broad singlet),
13.1-13 .7 (1H, broad).

EXAMPLE 13

5-{1-[2-(3-p-Fluorophenylureido)thiazol-4-yl]-1-ethoxycarbonylmethylene}rhodanine-3-acetic acid

Following a procedure similar to that described in Example 1, 1.91 g of the desired compound was prepared from 3.4 g of ethyl 2-(3-p-fluorophenylureido)thiazol-4-ylglyoxylate, 1.9 g of rhodanine-3-acetic acid, 1 g of ammonium chloride, 1 ml of 28% v/v aqueous ammonia and 50 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 228 to 253 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J = 7 Hz),
4.42 (2H, quartet, J = 7 Hz),
4.70 (2H, singlet),
7.18 (2H, triplet, J = 9 Hz),
7.50 (2H, doublet of doublets, J = 5 and 9 Hz),
7.70 (1H, singlet),
8.97 (1H, broad singlet, disappeared on adding deuterium oxide),
11.05 (1H, broad singlet, disappeared on adding deuterium oxide),
13.1-13.7 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 14

5-{1-[2-(3-p-Chlorophenylureido)thiazol-4-yl]-1-ethoxycarbonylmethylene}rhodanine-3-acetic acid

Following a procedure similar to that described in Example 1, 0.77 g of the desired compound was prepared from 3.54 g of ethyl 2-(3-p-chlorophenylureido)thiazol-4-ylglyoxylate, 1.9 g of rhodanine-3-acetic acid. 1 g of ammonium chloride, 1 ml of 28% v/v aqueous ammonia and 30 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 238 to 242 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:

1.34 (3H, triplet, J = 7 Hz),
4.42 (2H, quartet, J = 7 Hz),
4.70 (2H, singlet),
7.39 (2H, doublet, J = 9 Hz),
7.52 (2H, doublet, J = 9 Hz),
7.71 (1H, singlet),
9.08 (1H, broad singlet, disappeared on adding deuterium oxide),
11.08 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 15

5-{1-[2-(3-p-Bromophenylureido)thiazol-4-yl]-1-ethoxycarbonylmethylene}rhodanine-3-acetic acid

Following a procedure similar to that described in Example 1, the desired compound was prepared from 4 g of ethyl 2-(3-pbromophenylureido)thiazol-4-ylglyoxylate, 2 g of rhodanine-3-acetic acid, 1 g of ammonium chloride, 1 ml of 28% v/v aqueous ammonia and 50 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 251 to 258 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.33 (3H, triplet, J = 7 Hz),
4.42 (2H, quartet, J = 7 Hz),
4.69 (2H, singlet),
7.47 (2H, doublet, J = 9 Hz),
7.52 (2H, doublet, J = 9 Hz),
7.70 (1H, singlet),
9.11 (1H, broad singlet, disappeared on adding deuterium oxide),
11.11 (1H, broad singlet, disappeared on adding deuterium oxide),
13.1-13.7 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 16

5-{1-[2-[3-(3,4-Dichlorophenyl)ureido]thiazol-4-yl]-1-ethoxycarbonylmethylene}rhodanine-3-acetic acid hemihydrate

Following a procedure similar to that described in Example 1, the desired compound was prepared from 3.9 g of ethyl 2-[3-(3,4-dichlorophenyl)ureido]thiazol-4-ylglyoxylate, 1.9 g of rhodanine-3-acetic acid, 1 g of ammonium chloride, 1 ml of 28% v/v aqueous ammonia and 60 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 223 to 224 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J = 7 Hz),
4.42 (2H, quartet, J = 7 Hz),
4.70 (2H, singlet),
7.40 (1H, doublet of doublets J = 2 and 9 Hz),
7.58 (1H, doublet, J = 9 Hz),
7.73 (1H, singlet),
7.88 (1H, doublet, J = 2 Hz), 9.22 (1H, broad singlet),
11.21 (1H, broad singlet),
13.0-13.8 (1H, broad).

EXAMPLE 17

Piperidinium 5-(2-Tritylaminothiazol-4-ylmethylene)rhodanine-3-acetate

A mixture comprising 2.5 g of 2-tritylaminothiazole-4-carbaldehyde, 0.81 g of rhodanine-3-acetic acid, 1.1 g of piperidine and 25 ml of ethanol was stirred at room temperature for 7 hours. The crystalline product which

precipitated out was collected by filtration and washed with methanol, to obtain 2.7 g of the desired compound as a yellowish-brown powder.
Melting point: 210 to 215 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.52-1.61 (6H, multiplet),
2.92 (4H, broad triplet, J = 5 Hz),
4.24 (2H, singlet),
7.16-7.42 (17H, multiplet),
8.97 (1H, singlet).

EXAMPLE 18

Piperidinium 2,4-Dioxo-5-(2-tritylaminothiazol-4-ylmethylene)thiazolidine-3-acetate

Following a procedure similar to that described in Example 17, the desired compound was prepared from 2.3 g of 2-tritylaminothiazole-4-carbaldehyde, 0.9 g of 2,4-dioxothiazolidine-3-acetic acid, 0.9 g of piperidine and 20 ml of ethanol. The resulting product was a pale yellow powder having the following physical properties.
Melting point: 205 to 210 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.53-1.62 (6H, multiplet),
2.94 (4H, broad triplet, J = 5 Hz),
3.82 (2H, singlet),
7.16-7.41 (17H, multiplet),
8.91 (1H, singlet).

EXAMPLE 19

t-Butyl 2,4-dioxo-5-(2-tritylaminothiazol4-ylmethylene)thiazolidine-3-acetate

Following a procedure similar to that described in Example 17, the desired compound was prepared from 2 g of 2-tritylaminothiazole-4-carbaldehyde, 1.2 g of t-butyl 2,4-dioxothiazolidine-3-acetate, 0.88 g of piperidine and 20 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Softening point: 103 to 106 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.40 (9H, singlet),
4.21 (2H, singlet),
7.16-7.4 (17H, multiplet),
8.96 (1H, singlet).
Mass spectrum (m/e) : 583 (M^+)

EXAMPLE 20

5-(2-Tritylaminothiazol-4-ylmethylene)thiazolidine-2,4-dione

Following a procedure similar to that described in Example 17, the desired compound was prepared from 2 g of 2-tritylaminothiazole-4-carbaldehyde, 0.7 g of 2,4-thiazol- idinedione, 1 g of piperidine and 20 ml of ethanol. The resulting product was a pale brown powder having the following physical properties.
Melting point: 225 to 228 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
7.15-7.40 (17H, multiplet),
8.88 (1H, singlet),
11.99 (1H, broad singlet).
Mass spectrum (m/e) : 469 (M^+)

EXAMPLE 21

5-(2-Aminothiazol-4-ylmethylene)rhodanine-3-acetic acid 1/3 hydrate

A mixture comprising 2.2 g of piperidinium 5-(2-tritylaminothiazol-4-ylmethylene)rhodanine-3-acetate and 30 ml of a 4N dioxane solution of hydrogen chloride was stirred at room temperature for 30 minutes, and the resulting mixture was left to stand overnight. The crystalline product which precipitated out was collected by filtration and washed with dioxane, to give the desired compound as a brownish-orange powder.
Melting point: 244 to 246 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
3-4 (2H, broad),
4.70 (2H, singlet),
7. 50 (1H, singlet),
7. 51 (1H, singlet).

EXAMPLE 22

5-(2-Aminothiazol-4-ylmethylene)thiazolidine-2,4-dione hydrochloride

Following a procedure similar to that described in Example 21, the desired compound was prepared from 1.4 g of 5-(2-tritylaminothiazole-4-ylmethylene)thiazolidine-2,4-dione and 25 ml of a 4N dioxane solution of hydrogen chloride. The resulting product was a pale brown powder having the following physical properties.
Melting point: 280 to 288 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
4.8-6.9 (2H, broad, disappeared on adding deuterium oxide),
7.28 (1H, singlet),
7.41 (1H, singlet),
12.2 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 23

5-(2-Aminothiazol-4-ylmethylene)-2,4-dioxothiazolidine-3-acetic acid hydrochloride

Method A
A mixture comprising 2 g of t-butyl 2,4-dioxo-5-(2-tritylaminothiazol-4-ylmethylene)thiazolidine-3-acetate, 30 ml of a 4N dioxane solution of hydrogen chloride and 100 ml of acetic acid was heated at 80 °C for 3 hours. The resulting mixture was cooled to room temperature and the crystalline product which precipitated out was collected by filtration to give the desired compound in the form of a powder.

Method B
Following a procedure similar to that described in Example 21, the desired compound was prepared from 2.7 g of piperidinium 2,4-dioxo-5-(2-tritylaminothiazol-4-ylmethylene)thiazolidine-3-acetate and 30 ml of a 4N dioxane solution of hydrogen chloride. The resulting product was a pale brown powder having the following physical properties.
Melting point : 295 to 298 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
3.7-5.7 (2H, broad),
4.32 (2H, singlet),
7.39 (1H, singlet),
7.60 (1H, singlet).

EXAMPLE 24

5-[2-(3-Phenylureido)thiazol-4-ylmethylene]rhodanine-3-acetic acid

A mixture comprising 1 g of 2-(3-phenylureido)thiazole-4-carbaldehyde, 0.85 g of rhodanine-3-acetic acid, 0.76 g of piperidine and 15 ml of ethanol was stirred at room temperature for 2 hours, and the resulting mixture was left to stand overnight. The crystals which precipitated out were collected by filtration, dispersed in dilute aqueous hydrochloric acid, and washed, with stirring, for 30 minutes. The resulting crystalline product was recrystallized from a mixture of acetic acid and ethyl acetate, to give 0.78 g of the desired compound as an orange powder.

Melting point: 251 to 256 °C (with decomposition)

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:

4.72 (2H, singlet),
7.07 (1H, triplet, J = 8 Hz),
7.34 (2H, triplet, J = 8 Hz),
7.48 (2H, doublet, J = 8 Hz),
7.73 (1H, singlet),
7.95 (1H, singlet),
8.94 (1H, broad singlet),
10.87 (1H, broad singlet),
13-13.7 (1H, broad).

EXAMPLE 25

2,4-Dioxo-5-[2-(3-phenylureido)thiazol-4-ylmethylene]thiazolidine-3-acetic acid

Method A

Following a procedure similar to that described in Example 24, the desired compound was prepared from 1 g of 2-(3-phenylureido)thiazole-4-carbaldehyde, 0.78 g of 2,4-dioxothiazolidine-3-acetic acid, 0.76 g of piperidine and 20 ml of ethanol. The resulting product was a yellow powder having the physical properties set out below.

Method B

Following a procedure similar to that described in preparation 1, the desired compound was prepared from 0.6 g of 5-(2-aminothiazol-4-ylmethylene)-2,4-dioxothiazolidine-3-acetic acid hydrochloride, 0.75 g of phenyl isocyanate and 20 ml of hexamethylphosphoric triamide. The resulting product was a yellow powder having the following physical properties.

Melting point: 230 to 235 °C (with decomposition)

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:

4.35 (2H, singlet),
7.06 (1H, triplet, J = 8 Hz),
7.34 (2H, triplet, J = 8 Hz),
7.48 (2H, doublet, J = 8 Hz),
7.83 (1H, singlet),
7.87 (1H, singlet),
8.98 (1H, singlet),
10.76 (1H, singlet),
13-13.7 (1H, broad).

EXAMPLE 26

5-[2-(3-Phenylureido)thiazol-4-ylmethylene]rhodanine

Following a procedure similar to that described in Example 24, the desired compound was prepared from 1 g of 2-(3-phenylureido)thiazole-4-carbaldehyde, 0.6 g of rhodanine, 0.75 g of piperidine and 15 ml of ethanol. The resulting product was a yellow-brown powder having the following physical properties.

Melting point: over 300 °C (with decomposition)

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:

7.06 (1H, triplet, J = 8 Hz),

7.34 (2H, triplet, J = 8 Hz),
7.48 (2H, doublet, J = 8 Hz),
7.50 (1H, singlet),
7.85 (1H, singlet),
8.93 (1H, singlet),
10.80 (1H, singlet, disappeared on adding deuterium oxide),
13.55 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 27

Benzyl 5-[1-(2-aminothiazol-4-yl)-1-ethoxycarbonylmethylene]rhodanine-3-acetate

A mixture comprising 2 g of 5-[1-(2-aminothiazol-4-yl)- 1-ethoxycarbonylmethylene]rhodanine-3-acetic acid monohydrate, 3 g of benzyl bromide, 1.1 g of triethylamine and 10 ml of hexamethylphosphoric triamide was stirred at room temperature for 16 hours. The reaction mixture was acidified with dilute hydrochloric acid and then extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulphate and the solvent was evaporated off under reduced pressure. The residue was purified by silica gel column chromatography, using as eluent a 8:2:1 by volume mixture of hexane, ethyl acetate and acetic acid, to give the desired compound as yellow crystals.
Melting point: 177 to 179 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.30 (3H, triplet, J = 7 Hz),
4.37 (2H, quartet, J = 7 Hz),
4.84 (2H, singlet),
5.19 (2H, singlet),
7.21 (1H, singlet),
7.36 (5H, singlet),
7.64 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 28

5-[1-(2-Acetylaminothiazol-4-yl)-1-ethoxycarbonylmethylene]-2,4-dioxothiazolidine-3-acetic acid

A mixture comprising 0.6 g of crude 5-{1-ethoxycarbonyl-1-hydroxy-1-[2-(3-phenylureido)thiazol-4-yl]methyl}-2,4-dioxothiazolidine-3-acetic acid [prepared from 2.6 g of ethyl 2-(3-phenylureido)thiazol-4-ylglyoxylate 1.2 g of 2,4-dioxothiazolidine-3-acetic acid, 1.2 g of piperidine and 30 ml of ethanol by a procedure similar to that of Example 24], 0.5 g of acetic anhydride and 4 ml of pyridine was heated at 60 °C for 17 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulphate, and the solvent was evaporated off under reduced pressure. The resulting oil was purified by silica gel column chromatography, using as eluent a 8:2:0.5 to 7:3:0.5 by volume mixture of benzene, ethyl acetate and acetic acid, to give the desired compound as a yellow powder having the following physical properties.
Melting point: 288 to 290 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.32 (3H, triplet, J = 7 Hz),
2.22 (3H, singlet),
4.31 (2H, singlet),
4.39 (2H, quartet, J = 7 Hz),
7.63 (1H, singlet),
12.38 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 29

5-{1-[2-(3-Benzoylthioureido)thiazol-4-yl]-1-ethoxycarbonylmethylene}rhodanine-3-acetic acid 1/2 acetic acid 1/2 ammonia adduct

The reaction described in Example 1 was repeated, but using 1.5 g of ethyl 2-(3-benzoylthioureido)thiazol-4-ylglyoxylate, 0.79 g of rhodanine-3-acetic acid, 0.1 g of ammonium chloride, 0.4 ml of 28% v/v aqueous ammonia, and 20 ml of ethanol, to give the title compound as a yellow powder.
Melting point: 233-235°C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J=7 Hz),
1.91 (1.5H, singlet),
4.43 (2H, quartet, J=7 Hz),
4.67 (2H, singlet),
7.53 (2H, triplet, J=7 Hz),
7.65 (1H, triplet, J=7 Hz),
7.69 (1H, singlet),
8.01 (2H, doublet, J=7 Hz).

EXAMPLE 30

Methyl 5-{1-ethoxycarbonyl-1-[2-(3-phenylureido)thiazol-4-yl]methylene}rhodanine-3-acetate

A mixture comprising 5 g of 5-{1-ethoxycarbonyl-1-[2-(3 -phenylureido)thiazol-4-yl]methylene} rhodanine-3-acetic acid, 10 g of methanol and 75 ml of a 4N dioxane solution of hydrogen chloride was left to stand at room temperature for about 20 hours. The reaction mixture was then poured into water and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulphate, and the solvent was evaporated off under reduced pressure. The residue was purified by silica gel column chromatography using as eluent a 3:1 to 1:1 by volume mixture of hexane and ethyl acetate. The resulting yellow crystalline product had the following physical properties.
Melting point: 228 to 233 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.33 (3H, triplet, J = 7 Hz),
3.70 (3H, singlet),
4.42 (2H, quartet, J = 7 Hz),
4.81 (2H, singlet),
7.07 (1H, triplet, J = 8 Hz),
7.34 (2H, triplet, J = 8 Hz),
7.49 (2H, doublet, J = 8 Hz),
7.71 (1H, singlet),
8.95 (1H, singlet, disappeared on adding deuterium oxide),
11.03 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 31

Ethyl 5-{1-ethoxycarbonyl-1-[2-(3-phenylureido)thiazol-4-yl]methylene}rhodanine-3-acetate monohydrate

Following a procedure similar to that described in Example 30, the desired compound was prepared from 2 g of 5-{1-ethoxycarbonyl-1-[2-(3-phenylureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid, 6 g of ethanol and 30 ml of a 4N dioxane solution of hydrogen chloride. The resulting product was a yellow powder having the following physical properties.
Melting Point: 94 to 98 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.18 (3H, triplet, J = 7 Hz),
1.21 (3H, triplet, J = 7 Hz),
4.14 (2H, quartet, J = 7 Hz),
4.29 (2H, quartet, J = 7 Hz),
4.74 (2H, singlet),
7.05 (1H, triplet, J = 7 Hz),
7.28 (1H, singlet),
7.33 (2H, triplet, J = 7 Hz),
7.48 (2H, doublet, J = 7 Hz),
8.98 (1H, broad singlet, disappeared on adding deuterium oxide),
10.62 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 32

Isopropyl 5-{1-ethoxycarbonyl-1-[2-(3-phenylureido)thiazol-4-yl]methylene}rhodanine-3-acetate sesquihydrate

Following a procedure similar to that described in Example 27, the desired compound was prepared from 1 g of 5-{1-ethoxycarbonyl-1-[2-(3-phenylureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid, 0.5 g of isopropyl bromide, 0.25 g of triethylamine and 10 ml of hexamethylphosphoric triamide. The resulting yellow crystalline product had the following physical properties.
Melting Point: 113 to 116 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.21 (6H, doublet, J = 6 Hz),
1.33 (3H, triplet, J = 7 Hz),
4.42 (2H, quartet, J = 7 Hz),
4.75 (2H, singlet),
4.96 (1H, septet, J = 6 Hz),
7.07 (1H, triplet, J = 8 Hz),
7.34 (2H, triplet, J = 8 Hz),
7.49 (2H, doublet, J = 8 Hz),
7.71 (1H, singlet),
8.95 (1H, broad singlet, disappeared on adding deuterium oxide),
11.03 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 33

Benzyl 5-{1-ethoxycarbonyl-1-[2,(3-phenylureido)thiazol-4-yl]methylene}rhodanine-3-acetate

A mixture comprising 1 g of 5-{1-ethoxycarbonyl-1-[2-(3-phenylureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid, 0.25 g of triethylamine, 0.7 g of benzyl bromide and 10 ml of hexamethylphosphoric triamide was stirred at room temperature overnight. The reaction mixture was then poured into water and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulphate, and the solvent was evaporated off under reduced pressure. The residue was purified by silica gel column chromatography, using as eluent a 2:1 by volume mixture of hexane and ethyl acetate. The resulting product was a yellow powder having the following physical properties.
Melting point: 209 to 216 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.33 (3H, triplet, J = 7 Hz),
4.42 (2H, quartet, J = 7 Hz),
4.87 (2H, singlet),
5.20 (2H, singlet),
7.07 (1H, triplet, J = 7 Hz),
7.3-7.4 (7H, not defined),
7.49 (2H, multiplet),
7.72 (1H, singlet),
8.95 (1H, broad singlet, disappeared on adding deuterium oxide),
11.02 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 34

1-Isopropoxycarbonyloxyethyl 5-{1-ethoxycarbonyl-1-[2-(3-phenylureido)thiazol-4-yl]methylene}rhodanine-3-acetate

1 g of 5-{1-ethoxycarbonyl-1-[2-(3-phenylureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid and 0.65 g of 1,8-diazabicyclo[5.4.0]undec-7-ene were dissolved in 16 ml of dimethylacetamide and 8 ml of 1-iodoethyl isopropyl carbonate were added dropwise thereto with stirring under ice-cooling. The resulting mixture was

stirred for 4 hours under ice-cooling, and then at room temperature for 2 days. The reaction mixture was then poured into water and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulphate, the solvent was evaporated off under reduced pressure, and the residue was purified by silica gel column chromatography, using as eluent a 3:1 by volume mixture of hexane and ethyl acetate. The powdery product obtained after evaporating off the solvent was washed with a small amount of the above eluent mixture, to give the desired compound as a yellow powder.

Melting point: 188 to 190 °C

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.30 (3H, doublet, J = 6 Hz),
1.31 (3H, doublet, J = 6 Hz),
1.40 (3H, triplet, J = 7 Hz),
1.54 (3H, doublet, J = 5.5 Hz),
4.48 (2H, quartet, J = 7 Hz),
4.72 and 4.84 (2H, AB, J = 17 Hz),
4.90 (1H, septet, J = 6 Hz),
6.81 (1H, quartet, J = 5.5 Hz),
7.16 (1H, triplet, J = 7 Hz),
7.19 (1H, singlet),
7.36 (2H, triplet, J = 7 Hz),
7.48 (2H, doublet, J = 7 Hz),
7.8-8.0 (1H, broad, disappeared on adding deuterium oxide),
9.07 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 35

Sodium 5-[1-ethoxycarbonyl-1-[2-(3-phenylureido)thiazol-4-yl]methylene]rhodanine-3-acetate tetrahydrate

A mixture comprising 2.46 g of 5-[1-ethoxycarbonyl-1-[2-(3-diphenylureido)thiazol-4-yl]methylene]rhodanine-3-acetic acid, 0.54 g of sodium methoxide and 30 ml of absolute ethanol was stirred for 1 hour under ice-cooling, and then treated by ultrasonication at room temperature for 30 minutes. The reaction mixture was then poured into anhydrous diethyl ether, and the crystalline product which precipitated out was collected by filtration, to give the desired compound as a reddish-brown powder.

Melting point: over 300 °C

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.32 (3H, triplet, J = 7 Hz),
4.29 (2H, singlet),
4.35 (2H, quartet, J = 7 Hz),
6.75 (1H, triplet, J = 8 Hz),
7.04 (1H, singlet),
7.14 (2H, triplet, J = 8 Hz),
7.59 (2H, doublet, J = 8 Hz),
8.79 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 36

5-[1-Isobutoxycarbonyl-1-[2-(3-phenylureido)thiazol-4-yl]methylene]rhodanine-3-acetic acid

Following a procedure similar to that described in Example 1, the desired compound was prepared from 160 mg of isobutyl 2-(3-phenylureido)thiazol-4-ylglyoxylate, 90 mg of rhodanine-3-acetic acid, 50 mg of ammonium chloride, 0.05 ml of 28% v/v aqueous ammonia and 2 ml of ethanol. The resulting product was a yellow powder having the following physical properties.

Melting point: 235 to 239 °C (with decomposition)

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
0.93 (6H, doublet, J = 7 Hz),
2.03 (1H, septet, J = 7 Hz),
4.15 (2H, doublet, J = 7 Hz),
4.69 (2H, broad singlet),
7.07 (1H, triplet, J = 8 Hz),
7.34 (2H, triplet, J = 8 Hz),

7.49 (2H, doublet, J = 8 Hz),
7.66 (1H, singlet),
8. 96 (1H, broad singlet, disappeared on adding deuterium oxide),
11.03 (1H, broad singlet, disappeared on adding deuterium oxide),
13-13.7 (1H, broad, disappeared on adding deuterium oxide).

EXAMPLE 37

5-{1-Carboxy-1-[2-(3-phenylureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid 1/4 hydrate

Following a procedure similar to that described in preparation 1, the desired compound was prepared from 1 g of 5-[1-(2-aminothiazol-4-yl)-1-carboxymethylene]rhodanine-3-acetic acid, 3.9 g of phenyl isocyanate and 10 ml of hexamethylphosphoric triamide. The resulting product was a yellow powder having the following physical properties.
Melting Point: circa 225 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
4.63 (2H, singlet),
7.04 (1H, triplet, J = 8 Hz),
7.23 (1H, singlet),
7.32 (2H, triplet, J = 8 Hz),
7.48 (2H, doublet, J = 8 Hz),
8.92 (1H, singlet, disappeared on adding deuterium oxide),
10.3-10.8 (1H, broad, disappeared on adding deuterium oxide),
10.99 (1H, singlet, disappeared on adding deuterium oxide),
13.0-13.8 (1H, broad, disappeared on adding deuterium oxide).

EXAMPLE 38

5-{1-Ethoxycarbonyl-1-[2-(3-o-fluorophenylureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid 2/5 acetic acid adduct

Following a procedure similar to that described in Example 1, the desired compound was prepared from 1.7 g of ethyl 2-(3-o-fluorophenylureido)thiazol-4-ylglyoxylate, 0.96 g of rhodanine-3-acetic acid, 0.5 g of ammonium chloride, 0.5 ml of 28% v/v aqueous ammonia and 20 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 220 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J = 7 Hz),
1.91 (1.2H, singlet),
4.42 (2H, quartet, J = 7 Hz),
4.69 (2H, broad singlet),
7.13 (1H, doublet of doublets of doublets, J = 8, 5, and 2 Hz),
7.21 (1H, broad triplet, J = 8 Hz),
7.30 (1H, doublet of doublets of doublets, J = 11, 8, and 1.5 Hz),
7.72 (1H, singlet),
8.12 (1H, doublet of triplets, J = 2 and 8 Hz),
8.93 (1H, broad singlet),
11.30 (1H, broad singlet).

EXAMPLE 39

E and Z Isomers of Ethyl 5-{1-ethoxycarbonyl-1-[2-(3-o-fluorophenylureido)thiazol-4-yl]methylene}rhodanine-3-acetate

A mixture comprising 5 g of 5-{1-ethoxycarbonyl-1-[2-(3-o-fluorophenylureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid, 10 g of ethanol and 75 ml of a 4N dioxane solution of hydrogen chloride was left to stand

at room temperature for 5 days. At the end of this time, the reaction mixture was poured into water and extracted with ethyl acetate. The extract was then dried over anhydrous sodium sulphate, and the solvent was evaporated off under reduced pressure. The residue was recrystallized from a mixture of hexane and ethyl acetate (about 1:1 by volume). The resulting crystals were purified by silica gel column chromatography, using as eluent a 3:1 by volume mixture of hexane and ethyl acetate, to give the desired compound (a) as an orange powder.

Melting point: 93 to 100 °C

Thin-layer chromatography: Rf = circa 0.29 (developing solvent: 3:1 by volume mixture of hexane and ethyl acetate).

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:

1.18 (3H, triplet, J = 7 Hz),
1.21 (3H, triplet, J = 7 Hz),
4.14 (2H, quartet, J = 7 Hz),
4.29 (2H, quartet, J = 7 Hz),
4.74 (2H, singlet),
7.05-7.3 (3H, multiplet),
7.31 (1H, singlet),
8.08-8.16 (1H, multiplet),
8.93 (1H, broad singlet),
10.84 (1H, broad singlet).

The mother liquor from the recrystallization of the compound (a) was then concentrated by evaporation under reduced pressure and the residue was purified by silica gel column chromatography, using as eluent a 5:1 by volume mixture of hexane and ethyl acetate, to give the desired compound (b) as a yellow powder.

Melting point: 230 to 235 °C (with decomposition)

Thin-layer chromatograpy: Rf = circa 0.53 (developing solvent: 3:1 by volume mixture of hexane and ethyl acetate).

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:

1.20 (3H, triplet, J = 7 Hz),
1.33 (3H, triplet, J = 7 Hz),
4.17 (2H, quartet, J = 7 Hz),
4.42 (2H, quartet, J = 7 Hz),
4.79 (2H, singlet),
7.05-7.35 (3H, multiplet),
7.73 (1H, singlet),
8.08-8.16 (1H, multiplet),
8.91 (1H, broad singlet, disappeared on adding deuterium oxide),
11.31 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 40

5-{1-Ethoxycarbonyl-1-[2-(3-m-fluorophenylureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid hemihydrate

Following a procedure similar to that described in Example 1, the desired compound was prepared from 1.7 g of ethyl 2-(3-m-fluorophenylureido)thiazol-4-ylglyoxylate, 0.96 g of rhodanine-3-acetic acid, 0.5 g of ammonium chloride, 0.5 ml of 28% v/v aqueous ammonia and 20 ml of ethanol. The resulting product was an orange powder having the following physical properties.

Melting point: 193 to 197 °C

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:

1.34 (3H, triplet, J = 7 Hz),
4.42 (2H, quartet, J = 7 Hz),
4.70 (2H, singlet),
6.90 (1H, doublet of triplets, J = 2 and 8 Hz),
7.19 (1H, doublet of triplets, J = 7 and 1 Hz),
7.38 (1H, doublet of triplets, J = 7 and 8 Hz),
7.48 (1H, doublet of triplets, J = 11 and 2 Hz),
7.71 (1H, singlet),
9.16 (1H, broad singlet, disappeared on adding deuterium oxide),
11.11 (1H, broad singlet, disappeared on adding deuterium oxide),
13.0-13.7 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 41

E and Z Isomers of Ethyl 5-{1-ethoxycarbonyl-1-[2-(3-p-fluorophenylureido)thiazol-4-yl]methylene}rhodanine-3-acetate

Following reaction and separation procedures similar to those described in Examples 30 and 39, the desired compounds (a) and (b) were prepared from 4.04 g of 5-{1-ethoxycarbonyl-1-[2-(3-p-fluorophenylureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid, 8 g of ethanol and 60 ml of a 4N dioxane solution of hydrogen chloride. Compound (a) was a yellow powder having the following physical properties.
Softening point: 115 to 125 °C
Thin-layer chromatograpy: Rf = circa 0.70 (developing solvent: 1:1 by volume mixture of hexane and ethyl acetate).
Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm:
1.26 (3H, triplet, J = 7 Hz),
1.38 (3H, triplet, J = 7 Hz),
4.21 (2H, quartet, J = 7 Hz),
4.47 (2H, quartet, J = 7 Hz),
4.83 (2H, singlet),
7.13 (2H, triplet, J = 9 Hz),
7.59 (1H, singlet),
7.61 (2H, doublet of doublets, J = 9 and 5 Hz),
8.61 (1H, broad singlet),
10.45 (1H, broad singlet).
Compound (b) was a reddish-brown powder having the following physical properties.
Softening point: 110 to 115 °C
Thin-layer chromatograpy: Rf = circa 0.41 (developing solvent: 1:1 by volume mixture of hexane and ethyl acetate).
Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm:
1.23 (3H, triplet, J = 7 Hz),
1.26 (3H, triplet, J = 7 Hz),
4.18 (2H, quartet, J = 7 Hz),
4.32 (2H, quartet, J = 7 Hz),
4.76 (2H, singlet),
7.10 (2H, triplet, J = 9 Hz),
7.28 (1H, singlet),
7.58 (2H, doublet of doublets, J = 9 and 5 Hz),
8.75 (1H, broad singlet),
9.85 (1H, broad singlet).

EXAMPLE 42

Sodium 5-{1-ethoxycarbonyl-1-[2-(3-p-fluorophenylureido)thiazol-4-yl]methylene}rhodanine-3-acetate

Following a procedure similar to that described in Example 35, the desired compound was prepared from 1 g of 5-{1-ethoxycarbonyl-1-[2-(3-p-fluorophenylureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid, 0.24 g of sodium methoxide and 20 ml of absolute ethanol. The resulting product was a reddish-brown powder having the following physical properties.
Melting point: 187 to 200 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.31 (3H, triplet, J = 7 Hz),
4.25 (2H, singlet),
4.35 (2H, quartet, J = 7 Hz),
6.96 (2H, triplet, J = 9 Hz),
7.03 (1H, singlet),
7.59 (2H, doublet of doublets, J = 9 and 5 Hz),
8.86 (1H, broad singlet),

EXAMPLE 43

5-[1-[2-[3-(2,4-Difluorophenyl)ureido]-thiazol-4-yl]-1-ethoxycarbonylmethylene]rhodanine-3-acetic acid hemihydrate

Following a procedure similar to that described in Example 1, the desired compound was prepared from 1.8 g of ethyl 2-[3-(2,4-difluorophenyl)ureido]thiazol-4-ylglyoxylate, 0.96 g of rhodanine-3-acetic acid, 0.5 g of ammonium chloride, 0.5 ml of 28% v/v aqueous ammonia and 30 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 235 to 243 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J = 7 Hz),
4. 42 (2H, quartet, J = 7 Hz),
4.69 (2H, broad singlet),
7.10 (1H, broad triplet, J = 9 Hz),
7.37 (1H, doublet of doublets of doublets, J = 3, 9, and 11 Hz),
7.71 (1H, singlet),
8.06 (1H, doublet of triplets, J = 6 and 9 Hz),
8.87 (1H, broad doublet, J = 1 Hz, disappeared on adding deuterium oxide),
11.30 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 44

5-[1-Ethoxycarbonyl-1-[2-[3-(4-fluoro-3-nitrophenyl)ureido]thiazol-4-yl]methylene]rhodanine-3-acetic acid hemihydrate 1/2 acetic acid adduct

Following a procedure similar to that described in Example 1, 1.13 g of the desired compound was prepared from 2.3 g of ethyl 2-[3-(4-fluoro-3-nitrophenyl)ureido]thiazol-4-ylglyoxylate, 0.95 g of rhodanine-3-acetic acid, 0.5 g of ammonium chloride, 0.5 ml of 28% v/v aqueous ammonia and 30 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: circa 250 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J = 7 Hz),
1.91 (1.5H, singlet),
4.42 (2H, quartet, J = 7 Hz),
4.69 (2H, broad singlet),
7.58 (1H, doublet of doublets, J = 9 and 11 Hz),
7.74 (1H, singlet),
7.75-7.80 (1H, multiplet),
8.43 (1H, doublet of doublets, J = 6 and 3 Hz),
9.40 (1H, broad singlet, disappeared on adding deuterium oxide),
11.35 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 45

5-[1-Ethoxycarbonyl-1-[2-[3-(2,4,6-trifluorophenyl)ureido]thiazol-4-yl]methylene]rhodanine-3-acetic acid dihydrate

Following a procedure similar to that described in Example 1, 0.58 g of the desired compound was prepared from 700 mg of ethyl 2-[3-(2,4,6-trifluorophenyl)ureido]thiazol-4-ylglyoxylate, 350 mg of rhodanine-3-acetic acid, 190 mg of ammonium chloride, 0.2 ml of 28 % v/v aqueous ammonia and 10 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 183 to 187 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.33 (3H, triplet, J = 7 Hz),
4.41 (2H, quartet, J = 7 Hz),

4.69 (2H, broad singlet),
7.32 (2H, doublet of doublets, J = 9 and 8 Hz),
7.69 (1H, singlet),
8.38 (1H, broad singlet, disappeared on adding deuterium oxide),
11.60 (1H, broad singlet, disappeared on adding deuterium oxide),
13.0-13.7 (1H, broad, disappeared on adding deuterium oxide).

EXAMPLE 46

5-{1-Ethoxycarbonyl-1-[2-[3-(3,4,5-trimethoxyphenyl)ureido]thiazol-4-yl]methylene}rhodanine-3-acetic acid sesquihydrate

Following a procedure similar to that described in Example 1, the desired compound was prepared from 1.1 g of ethyl 2-[3-(3,4,5-trimethoxyphenyl)ureido]thiazol-4-ylglyoxylate, 0.48 g of rhodanine-3-acetic acid, 0.25 g of ammonium chloride, 0.25 ml of 28% v/v aqueous ammonia and 20 ml of ethanol, in the form of brown prismatic crystals having the following physical properties.
Melting point: 173 to 180 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J = 7 Hz),
3.63 (3H, singlet),
3.78 (6H, singlet),
4.42 (2H, quartet, J = 7 Hz),
4.69 (2H, broad singlet),
6.81 (2H, singlet),
7.70 (1H, singlet),
8.92 (1H, broad singlet, disappeared on adding deuterium oxide),
11.04 (1H, broad singlet, disappeared on adding deuterium oxide),
13.1-13.8 (1H, broad, disappeared on adding deuterium oxide).

EXAMPLE 47

5-{1-[2-(3-o-Chlorophenylureido)thiazol-4-yl]-1-ethoxycarbonylmethylene}rhodanine-3-acetic acid monohydrate

Following a procedure similar to that described in Example 1, the desired compound was prepared from 1.77 g of ethyl 2-(3-o-chlorophenylureido)thiazol-4-ylglyoxylate, 0.95 g of rhodanine-3-acetic acid, 0.5 g of ammonium chloride, 0.5 ml of 28% v/v aqueous ammonia and 25 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 230 to 238 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J = 7 Hz),
4. 42 (2H, quartet , J = 7 Hz),
4. 69 (2H, broad singlet),
7. 13 (1H, doublet of triplets, J = 8 and 1. 5 Hz),
7.36 (1H, doublet of triplets, J = 8 and 1.5 Hz),
7.52 (1H, doublet of doublets, J = 8 and 1.5 Hz),
7.72 (1H, singlet),
8.17 (1H, doublet of doublets, J = 8 and 1.5 Hz),
8.78 (1H, broad singlet, disappeared on adding deuterium oxide),
11.64 (1H, broad singlet, disappeared on adding deuterium oxide),
13-14 (1H, broad, disappeared on adding deuterium oxide).

EXAMPLE 48

5-{1-Ethoxycarbonyl-1-[2-(3-p-tolylureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid

Following a procedure similar to that described in Example 1, the desired compound was prepared using 4.8 g of ethyl 2-(3-p-tolylureido)thiazol-4-ylglyoxylate, 2.5 g of rhodanine-3-acetic acid, 1.5 g of ammonium chloride, 1.5 ml of 28% v/v aqueous ammonia and 50 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 240 to 245 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J = 7 Hz),
2.27 (3H, singlet),
4.42 (2H, quartet, J = 7 Hz),
4.69 (2H, broad singlet),
7.15 (2H, doublet, J = 8 Hz),
7.37 (2H, doublet, J = 8 Hz),
7.69 (1H, singlet),
8.86 (1H, broad singlet, disappeared on adding deuterium oxide),
10.99 (1H, broad singlet, disappeared on adding deuterium oxide),
13.0-13.8 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 49

5-{1-Ethoxycarbonyl-1-[2-[3-(2,6-xylyl)ureido]thiazol-4-yl]-methylene}rhodanine-3-acetic acid

Following a procedure similar to that described in Example 1, the desired compound was prepared using 1.74 g of ethyl 2-[3-(2,6-xylyl)ureido]thiazol-4-ylglyoxylate, 0.96 g of rhodanine-3-acetic acid, 0.5 g of ammonium chloride, 0.5 ml of 28% v/v aqueous ammonia and 20 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 240 to 245 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.33 (3H, triplet, J = 7 Hz),
2.21 (6H, singlet),
4.41 (2H, quartet, J = 7 Hz),
4.69 (2H, broad singlet),
7.12 (3H, singlet),
7.65 (1H, singlet),
8.14 (1H, broad singlet, disappeared on adding deuterium oxide),
11.24 (1H, broad singlet, disappeared on adding deuterium oxide),
12.9-13.9 (1H, broad, disappeared on adding deuterium oxide).

EXAMPLE 50

5-{1-Ethoxycarbonyl-1-[2-(3-p-nitrophenylureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid bis(dimethylformamide) adduct

Following a procedure similar to that described in Example 1, the desired compound was prepared from 3.7 g of ethyl 2-(3-p-nitrophenylureido)thiazol-4-ylglyoxylate, 1.9 g of rhodanine-3-acetic acid, 1 g of ammonium chloride, 1 ml of 28% v/v aqueous ammonia and 40 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 285 to 290 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J = 7 Hz),
2.73 (6H, singlet),
2.89 (6H, singlet),
4.42 (2H, quartet, J = 7 Hz),
4.70 (2H, broad singlet),
7.75 (2H, doublet, J = 9 Hz),
7.75 (1H, singlet),
7.95 (2H, singlet),
8.25 (2H, doublet, J = 9 Hz),
9. 64 (1H, broad singlet, disappeared on adding deuterium oxide),
1.30 (1H, broad singlet, disappeared on adding deuterium oxide),

13.0-13.8 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 51

5-{1-Ethoxycarbonyl-1-[2-(3-o-trifluoromethylphenylureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid

Following a procedure similar to that described in Example 1, the desired compound was prepared from 3.9 g of ethyl 2-(3-o-trifluoromethylphenylureido)thiazol-4-ylglyoxylate, 1.9 g of rhodanine-3-acetic acid, 1 g of ammonium chloride, 1 ml of 28% v/v aqueous ammonia and ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 160 to 170 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
Melting point: 245 to 250 °C with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J = 7Hz),
4.42 (2H, quartet, J = 7 Hz),
4.70 (2H, broad singlet),
7.39 (1H, triplet, J = 8 Hz),
7.65-7.75 (1H, not defined),
7.72 (1H, singlet),
7.75 (1H, doublet, J = 8 Hz),
7.96 (1H, doublet, J = 8 Hz),
8.54 (1H, broad singlet, disappeared on adding deuterium oxide),
11.59 (1H, broad singlet, disappeared on adding deuterium oxide),
12.9-13.9 (1H, broad, disappeared on adding deuterium oxide).

EXAMPLE 52

5-{1-Ethoxycarbonyl-1-[2-(3-p-trifluoromethylphenylureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid

Following a procedure similar to that described in Example 1, the desired compound was prepared from 3.9 g of ethyl 2-(3-p-trifluoromethylphenylureido)thiazol-4-ylglyoxylate, 1.9 g of rhodanine-3-acetic acid, 1 g of ammonium chloride, 1 ml of 28% v/v aqueous ammonia and 30 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 160 to 170 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J = 7 Hz),
4.42 (2H, quartet, J = 7 Hz),
4.70 (2H, broad singlet),
7.70 (4H, singlet),
7.73 (1H, singlet),
9.34 (1H, broad singlet, disappeared on adding deuterium oxide),
11.17 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 53

5-{1-[2-(3,3-Diphenylureido)thiazol-4-yl]-1-ethoxycarbonylmethylene}rhodanine-3-acetic acid

Following a procedure similar to that described in Example 1, the desired compound was prepared from 130 mg of ethyl 2-(3,3-diphenylureido)thiazol-4-ylglyoxylate, 60 mg of rhodanine-3-acetic acid, 30 mg of ammonium chloride, 0.03 ml of 28% v/v aqueous ammonia and 5 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 205 to 230 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.32 (3H, triplet, J = 7 Hz),
4.40 (2H, quartet, J = 7 Hz),

4.66 (2H, broad singlet),
7.27-7.34 (6H, multiplet),
7.44 (4H, triplet, J = 8 Hz),
7.69 (1H, singlet),
11.18 (1H, broad singlet, disappeared on adding deuterium oxide),
12.5-14.0 (1H, broad, disappeared on adding deuterium oxide).

EXAMPLE 54

5-[1-Ethoxycarbonyl-1-[2-(3-methylureido)thiazol-4-yl]methylene]rhodanine-3-acetic acid

Following a procedure similar to that described in Example 1, the desired compound was prepared from 3.17 g of ethyl 2-(3-methylureido)thiazol-4-ylglyoxylate, 2.2 g of rhodanine-3-acetic acid, 1.2 g of ammonium chloride, 1.2 ml of 28% v/v aqueous ammonia and 50 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 241 to 245 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.32 (3H, triplet, J = 7 Hz),
2.73 (3H, doublet, J = 5 Hz, converted to singlet on adding deuterium oxide),
4.40 (2H, quartet, J = 7 Hz),
4.68 (2H, broad singlet),
6.47 (1H, broad doublet, J = 5 Hz, disappeared on adding deuterium oxide),
7.60 (1H, singlet),
11.03 (1H, broad singlet, disappeared on adding deuterium oxide),
13.0-13.7 (1H, broad, disappeared on adding deuterium oxide).

EXAMPLE 55

5-[1-[2-(3-Benzylureido)thiazol-4-yl]-1-ethoxycarbonylmethylene]rhodanine-3-acetic acid dihydrate

Following a procedure similar to that described in Example 1, the desired compound was prepared from 1.67 g of ethyl 2-(3-benzylureido)thiazol-4-ylglyoxylate, 0.95 g of rhodanine-3-acetic acid, 0.5 g of ammonium chloride, 0.5 ml of 28% v/v aqueous ammonia and 25 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 220 to 225 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.32 (3H, triplet, J = 7 Hz),
4.35-4.45 (2H, not defined),
4.39 (2H, broad singlet),
4.68 (2H, broad singlet),
7.08 (1H, broad triplet, J = 6 Hz, disappeared on adding deuterium oxide),
7.2-7.4 (5H, multiplet),
7.62 (1H, singlet),
11.06 (1H, broad singlet, disappeared on adding deuterium oxide),
13.0-13.8 (1H, broad, disappeared on adding deuterium oxide).

EXAMPLE 56

5-[1-[2-(3-Cyclohexylureido)thiazol-4-yl]-1-ethoxycarbonylmethylene]rhodanine-3-acetic acid

Following a procedure similar to that described in Example 1, the desired compound was prepared using 1 g of ethyl 2-(3-cyclohexylureido)thiazol-4-ylglyoxylate, 0.58 g of rhodanine-3-acetic acid, 0.3 g of ammonium chloride, 0.3 ml of 28% v/v aqueous ammonia and 10 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 245 to 248 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:

1.15-1.45 (5H, multiplet),
1.32 (3H, triplet, J = 7 Hz),
1.45-1.6 (1H, multiplet),
1.6-1.75 (2H, multiplet),
1.75-1.9 (2H, multiplet),
3.42-3.62 (1H, multiplet),
4.40 (2H, quartet, J = 7 Hz),
4.68 (2H, singlet),
6.56 (1H, broad doublet, J = 8 Hz),
7.60 (1H, singlet),
10.65 (1H, broad singlet),
12.9-13.9 (1H, broad).

EXAMPLE 57

5-[(2E)-3-[2-(3-p-bromophenylureido)thiazol-4-yl]allylidene]rhodanine-3-acetic acid hemihydrate

Following a procedure similar to that described in Example 1, the desired compound was prepared using 0.4 g of (E)-3-[2-(3-p-bromophenylureido)thiazol-4-yl]acrylaldehyde, 0.2 g of rhodanine-3-acetic acid, 0.15 g of ammonium chloride, 0.15 ml of 28% v/v aqueous ammonia and 10 ml of ethanol. The resulting product was a brownish-orange powder having the following physical properties.
Melting point: 215 to 220 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
4.70 (2H, broad singlet),
6.89 (1H, doublet of doublets, J = 15 and 12 Hz),
7.34 (1H, doublet, J = 15 Hz),
7.47 and 7.50 (4H, A_2B_2, J = 9 Hz),
7.55 (1H, singlet),
7.64 (1H, doublet, J = 12 Hz),
9.06 (1H, broad singlet, disappeared on adding deuterium oxide),
10.8-11.2 (1H, broad, disappeared on adding deuterium oxide),
13.0-13.8 (1H, broad, disappeared on adding deuterium oxide).

EXAMPLE 58

5-[2-(3-Phenylureido)thiazol-4-ylmethylene]thiazolidine-2,4-dione 1/3 hydrate

Following a procedure similar to that described in Example 1, the desired compound was prepared from 1.1 g of 2-(3-phenylureido)thiazole-4-carbaldehyde, 0.52 g of 2,4-thiazolidinedione, 0.6 g of ammonium chloride, 0.6 ml of 28% v/v aqueous ammonia and 20 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: over 300 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
7.06 (1H, triplet, J = 8 Hz),
7.33 (2H, triplet, J = 8 Hz),
7.48 (2H, doublet of doublets, J = 8 and 1 Hz),
7.63 (1H, singlet),
7.78 (1H, singlet),
8.96 (1H, broad singlet, disappeared on adding deuterium oxide),
10.70 (1H, broad singlet, disappeared on adding deuterium oxide),
12.32 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 59

5-[1-(2-Dimethylaminothiazol-4-yl)-1-ethoxycarbonylmethylene]rhodanine-3-acetic acid

The reaction described in Example 1 was repeated, but using 0.5 g of ethyl 2-dimethylaminothiazol-4-ylglyoxylate, 0.35 g of rhodanine-3-acetic acid. 0.26 g of ammonium chloride, 0.3 ml of 28% v/v aqueous ammonia, and 5 ml of ethanol, to give the title compound as orange needles.
Melting point: 275 to 278°C (with decomposition).
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.32 (3H, triplet J=7 Hz),
3.15 (6H, singlet),
4.39 (2H, quartet, J=7 Hz),
4.67 (2H, singlet),
7.34 (1H, singlet),
13.2-13.6 (1H, broad).

EXAMPLE 60

5-(2-Diethylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid

The reaction described in Example 1 was repeated, but using 1.2 g of 2-diethylaminothiazole-4-carbaldehyde, 1 g of rhodanine-3-acetic acid, 0.6 g of ammonium chloride, 0.8 ml of 28% v/v aqueous ammonia, and 25 ml of ethanol, to give the title compound as yellowish-brown needles.
Melting point: 257 to 260°C (with decomposition).
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.23 (6H, triplet, J=7 Hz),
3.52 (4H, quartet, J=7 Hz),
4.70 (2H, singlet),
7.56 (1H, singlet),
7.59 (1H, singlet),
13.2-13.5 (1H, broad).

EXAMPLE 61

Ethyl 5-{1-ethoxycarbonyl-1-[2-(3-phenylthioureido)thiazol-4-yl]methylene}rhodanine-3-acetate

A mixture comprising 10 g of 5-{1-ethoxycarbonyl-1-[2-(3-phenylthioureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid, 20 g of ethanol and 150 ml of a 4N dioxane solution of hydrogen chloride was left to stand at room temperature for 4.5 days. The reaction mixture was then poured into water and extracted with ethyl acetate. The extract was washed with aqueous potassium carbonate solution and then with aqueous sodium chloride solution, and was then dried over anhydrous sodium sulphate. The solvent was evaporated off under reduced pressure, and the residue was purified by silica gel column chromatography, using as eluent a 1:1 by volume mixture of hexane and ethyl acetate. The resulting crystalline product was recrystallised from a 1:5 by volume mixture of hexane and ethyl acetate, to give a yellow powder having the following physical properties.
Melting point: 195 to 200 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.17 (3H, triplet, J = 7 Hz),
1.21 (3H, triplet, J = 7 Hz),
4.13 (2H, quartet, J = 7 Hz),
4.29 (2H, quartet, J = 7 Hz),
4.75 (2H, broad singlet),
6.8-7.9 (6H, multiplet).

EXAMPLE 62

Ethyl 5-{1-[2-(3-p-chlorophenylthioureido)thiazol-4-yl]-1-ethoxycarbonylmethylene}rhodanine-3-acetate

A mixture comprising 4.8 g of 5-{1-[2-(3-p-chlorophenylthioureido)thiazol-4-yl]-1-ethoxycarbonylmethylene}rhodanine-3-acetic acid, 10 g of ethanol and 50 ml of a 4N dioxane solution of hydrogen chloride was left to stand at room temperature for 4.5 days. The reaction mixture was then poured into water and extracted

with ethyl acetate. The extract was washed with aqueous sodium chloride solution, and was then dried over anhydrous sodium sulphate. The solvent was evaporated off under reduced pressure, and the residue was recrystallized from a circa 1:1 by volume mixture of hexane and ethyl acetate. The resulting product was an orange powder having the following physical properties.
Melting point: 175 to 177 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.17 (6H, triplet, J = 7 Hz),
4.13 (2H, quartet, J = 7 Hz),
4.30 (2H, quartet, J = 7 Hz),
4.76 (2H, broad singlet),
7.0-7.9 (5H, multiplet).

EXAMPLE 63

5-{1-Ethoxycarbonyl-1-[2-(3-o-fluorophenylthioureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid 1/4 hydrate

Following a procedure similar to that described in Example 1, the desired compound was prepared from 7 g of ethyl 2-(3-o-fluorophenylthioureido)thiazol-4-ylglyoxylate, 3.8 g of rhodanine-3-acetic acid, 2 g of ammonium chloride, 2 ml of 28% v/v aqueous ammonia and 100 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 187 to 200 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J = 7 Hz),
4.42 (2H, quartet, J = 7 Hz),
4.69 (2H, broad singlet),
7.2-7.37 (3H, multiplet),
7.67 (1H, singlet),
7.87 (1H, broad triplet, J = 8 Hz),
10.05 (1H, broad singlet, disappeared on adding deuterium oxide),
12.1-12.5 (1H, broad, disappeared on adding deuterium oxide).

EXAMPLE 64

5-{1-Ethoxycarbonyl-1-[2-(3-p-fluorophenylthioureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid

Following a procedure similar to that described in Example 1, the desired compound was prepared from 550 mg of ethyl 2-(3-p-fluorophenylthioureido)thiazol-4-ylglyoxylate, 290 mg of rhodanine-3-acetic acid, 150 mg of ammonium chloride, 0.15 ml of 28% v/v aqueous ammonia and 10 ml of ethanol. The resulting product was in the form of yellow acicular crystals having the following physical properties.
Melting point: 220 to 225 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet , J = 7 Hz),
4.42 (2H, quartet, J = 7 Hz),
4.70 (2H, broad singlet),
7.25 (2H, triplet, J = 9 Hz),
7.61 (2H, doublet of doublets, J = 5 and 9 Hz),
7.66 (1H, singlet),
10.29 (1H, broad singlet, disappeared on adding deuterium oxide),
11.9-12.2 (1H, broad, disappeared on adding deuterium oxide),
13.15-13.7 (1H, broad, disappeared on adding deuterium oxide).

EXAMPLE 65

5-(2-Anilinothiazol-4-ylmethylene)rhodanine-3-acetic acid

Following a procedure similar to that described in Example 24, the desired compound was prepared from 440 mg of 2-anilinothiazole-4-carbaldehyde, 412 mg of rhodanine-3-acetic acid, 0.5 ml of piperidine and 10 ml of ethanol. The resulting product was a yellowish-brown powder having the following physical properties.
Melting point: 242 to 246 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
4.87 (2H, broad singlet),
7.10 (1H, triplet, J = 8 Hz),
7.42 (2H, triplet, J = 8 Hz),
7.59 (1H, singlet),
7.63 (1H, singlet),
7.78 (2H, doublet, J = 8 Hz),
9.63 (1H, broad singlet).

EXAMPLE 66

Ethyl 5-(2-anilinothiazol-4-ylmethylene)rhodanine-3-acetate

Following a procedure similar to that described in Example 30, the desired compound was prepared from 1 g of 5-(2-anilinothiazol-4-ylmethylene)rhodanine-3-acetic acid, 2 g of ethanol and 10 ml of a 4N dioxane solution of hydrogen chloride. The resulting product was a yellow powder having the following physical properties.
Melting point: 212 to 215 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.21 (3H, triplet, J = 7 Hz),
4.17 (2H, quartet, J = 7 Hz),
4.81 (2H, singlet),
7.05 (1H, triplet, J = 8 Hz),
7.37 (2H, triplet, J = 8 Hz),
7.68 (1H, singlet),
7.71 (2H, doublet, J = 8 Hz),
7.80 (1H, singlet),
10.54 (1H, singlet, disappeared on adding deuterium oxide).

EXAMPLE 67

1-Isopropoxycarbonyloxyethyl 5-(2-anilinothiazol-4-ylmethylene)rhodanine-3-acetate

Following a procedure similar to that described in Example 34, the desired compound was prepared from 1 g of 5-(2-anilinothiazol-4-ylmethylene)rhodanine-3-acetic acid, 0.5 g of 1,8-diazabicyclo[5.4.0]undec-7-ene, 4.5 g of 1-iodoethyl isopropyl carbonate and 16 ml of dimethylacetamide. The resulting product was a yellowish-green powder having the following physical properties.
Melting point: 166 to 169 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.24 (6H, doublet, J = 6 Hz),
1.46 (3H, doublet, J = 5 Hz),
4.79 (1H, septet, J = 6 Hz),
4.8-4.95 (2H, not defined), 6.67 (1H, quartet, J = 5 Hz),
7.05 (1H, triplet, J = 8 Hz),
7.36 (2H, triplet, J = 8 Hz),
7.68 (1H, singlet),
7.71 (2H, doublet, J = 8 Hz),
7.81 (1H, singlet),
10.55 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 68

Sodium 5-(2-anilinothiazol-4-ylmethylene)rhodanine-3-acetate

Following a procedure similar to that described in Example 35, the desired compound was prepared from 1 g of 5-(2-anilinothiazol-4-ylmethylene)rhodanine-3-acetic acid, 280 mg of sodium methoxide and 20 ml of ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: 280 to 295 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
4.31 (2H, singlet),
7.03 (1H, triplet, J = 8 Hz),
7.35 (2H, triplet, J = 8 Hz),
7.51 (1H, singlet),
7.69 (1H, singlet),
7.74 (2H, doublet, J = 8 Hz),
10.70 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 69

5-[2-(o-toluidino)thiazol-4-ylmethylene]rhodanine-3-acetic acid

Following a procedure similar to that described in Example 1, the desired compound was prepared from 1.12 g of 2-(o-toluidino)thiazole-4-carbaldehyde, 0.87 g of rhodanine-3-acetic acid, 0.5 g of ammonium chloride, 0.5 ml of 28% v/v aqueous ammonia and 15 ml of ethanol. The resulting product was an orange powder having the following physical properties.
Melting point: 247 to 249.5 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
2.30 (3H, singlet),
4.70 (2H, singlet),
7.08 (1H, broad triplet, J = 8 Hz),
7.24 (2H, broad triplet, J = 8 Hz),
7.62 (1H, singlet),
7.72 (1H, singlet),
7.95 (1H, broad doublet, J = 8 Hz),
9.67 (1H, broad singlet),
13.1-13.6 (1H, broad).

EXAMPLE 70

5-[(2E)-3-(2-Anilinothiazol-4-yl)allylidene]rhodanine-3-acetic acid

Following a procedure similar to that described in Example 1, the desired compound was prepared from 0.4 g of (2E)-3-(2-anilinothiazol-4-yl)acrylaldehyde, 0.29 g of rhodanine-3-acetic acid, 0.22 g of ammonium chloride, 0.2 ml of 28% v/v aqueous ammonia and 10 ml of ethanol. The resulting product was a reddish-brown powder having the following physical properties.
Melting point: 244 to 248 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
4.70 (2H, broad singlet),
6.91 (1H, doublet of doublets, J = 15 and 12 Hz),
7.00 (1H, triplet, J = 7 Hz),
7.28 (1H, doublet, J = 15 Hz),
7.37 (1H, singlet),
7.37 (2H, triplet, J = 7 Hz),
7.64 (1H, doublet, J = 12 Hz),
7.67 (2H, doublet, J = 7 Hz),
10.38 (1H, broad singlet, disappeared on adding deuterium oxide).

EXAMPLE 71

5-(2-Diphenylmethylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid

Following a procedure similar to that described in Example 1, the desired compound was prepared from 1.95 g of 2-diphenylmethylaminothiazole-4-carbaldehyde, 1.32 g of rhodanine-3-acetic acid, 0.4 g of ammonium chloride, 0.4 ml of 28% v/v aqueous ammonia and 20 ml of ethanol. The resulting product was a reddish-brown powder having the following physical properties.

Melting point: 227 to 230 °C (with decomposition)

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
4.66 (2H, singlet),
6.13 (1H, doublet, J = 7 Hz, converted to 6.13 (1H, singlet) on adding deuterium oxide),
7.2-7.4 (10H, multiplet),
7.48 (1H, singlet),
7.54 (1H, singlet),
8.99 (1H, doublet, J = 7 Hz, disappeared on adding deuterium oxide),
13.0-13.7 (1H, broad, disappeared on adding deuterium oxide).

EXAMPLE 72

Ethyl 5-(2-diphenylmethylaminothiazol-4-ylmethylene)rhodanine-3-acetate

Following a procedure similar to that described in Example 30, the desired compound was prepared from 0.6 g of 5-(2-diphenylmethylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid, 7.7 g of ethanol and 15 ml of a 4N dioxane solution of hydrogen chloride. The resulting product was a greenish-yellow powder having the following physical properties.

Melting point: 196 to 199 °C (with decomposition)

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.19 (3H, triplet, J = 7 Hz),
4.15 (2H, quartet, J = 7 Hz),
4.76 (2H, singlet),
6.13 (1H, doublet , J = 7 Hz, converted to 6.12 (1H, singlet) on adding deuterium oxide),
7.22-7.43 (10H, multiplet),
7.50 (1H, singlet),
7.55 (1H, singlet),
8.99 (1H, doublet, J = 7 Hz, disappeared on adding deuterium oxide).

EXAMPLE 73

Sodium 5-(2-diphenylmethylaminothiazol-4-ylmethylene)rhodanine-3-acetate monohydrate

Following a procedure similar to that described in Example 35, the desired compound was prepared from 200 mg of 5-(2-diphenylmethylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid, 24.5 mg of sodium methoxide and 6 ml of ethanol. The resulting product was a yellow powder having the following physical properties.

Melting point: 181 to 194 °C (with decomposition)

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
4.20 (2H, singlet),
6.15 (1H, doublet, J = 8 Hz),
7.22-7.45 (12H, multiplet),
8.95 (1H, doublet, J = 8 Hz).

EXAMPLE 74

5-{1-[2-Bis(p-fluorophenyl)methylaminothiazol-4-yl]-1-ethoxycarbonylmethylene}rhodanine-3-acetic acid

Following a procedure similar to that described in Example 1, the desired compound was prepared from 342 mg of ethyl 2-bis(p-fluorophenyl)methylaminothiazol-4-ylglyoxylate, 164 mg of rhodanine-3-acetic acid, 0.11 g of ammonium chloride, 0.2 ml of 28% v/v aqueous ammonia and 2 ml of ethanol, as red prismatic crystals. The product had the following physical properties.
Melting point: 245 to 247 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.29 (3H, triplet, J = 7 Hz),
4.35 (2H quartet, J = 7 Hz),
4.63 (2H, singlet),
6.08 (1H, doublet, J = 6 Hz),
7.14-7.23 (4H, multiplet),
7.26 (1H, singlet),
7.37-7.45 (4H, multiplet),
9.03 (1H, doublet, J = 6 Hz),

EXAMPLE 75

5-[1-Ethoxycarbonyl-1-(2-phthalimidothiazol-4-yl)methylene]rhodanine-3-acetic acid hemihydrate

0.7 g of phthaloyl dichloride was added dropwise under ice-cooling to a solution of 1.19 g of 5-[1-(2-aminothiazol-4-yl)-1-ethoxycarbonylmethylene]rhodanine-3-acetic acid in 8 ml of tetrahydrofuran. The resulting mixture was stirred for 6 hours under ice-cooling and then heated at 60 °C for 4 hours. The crystals which precipitated out after cooling were collected by filtration and recrystallized from ethanol. The resulting product was a yellow powder having the following physical properties.
Melting point: circa 300 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.36 (3H, triplet, J = 7 Hz),
4.46 (2H, quartet, J = 7 Hz),
4.71 (2H, broad singlet),
7.98 (2H, doublet of doublets, J = 5 and 3 Hz),
8.05-8.15 (2H, not defined),
8.10 (1H, singlet),
12.9-13.8 (1H, broad, disappeared on adding deuterium oxide).

EXAMPLE 76

5-[2-(p-Fluoroanilino)thiazol-4-ylmethylene]rhodanine-3-acetic acid

The reaction described in Example 1 was repeated, but using 1 g of 2-(p-fluoroanilino)thiazole-4-carbaldehyde, 0.85 g of rhodanine-3-acetic acid, 0.5 g of ammonium chloride, 0.5 ml of 28% v/v aqueous ammonia, and 10 ml of ethanol, to give the title compound as an orange powder:
Melting point: 263.5 to 226 °C (with decomposition).
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
4.71 (2H, singlet),
7.19 (2H, triplet, J=9 Hz),
7.65 (1H, singlet),
7.71 (2H, doublet of doublets, J=9 and 5 Hz),
7.78 (1H, singlet),
10.54 (1H, broad singlet, disappeared on adding deuterium oxide),
13.0-13.8 (1H, broad, disappeared on adding deuterium oxide).

EXAMPLE 77

5-[2-(p-Anisidino)thiazol-4-ylmethylene]rhodanine-3-acetic acid

The reaction described in Example 1 was repeated, but using 1 g of 2-(p-anisidino)thiazole-4-carbaldehyde,

0.8 g of rhodanine-3-acetic acid, 0.5 g of ammonium chloride, 0.5 ml of 28% v/v aqueous ammonia, and 10 ml of ethanol, to give the title compound as an orange powder.
Melting point: 197 to 202 °C.
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
3.76 (3H, singlet),
4.72 (2H, singlet),
6.93 (2H, doublet, J=9 Hz),
7.60 (2H, doublet, J=9 Hz),
7.63 (1H, singlet),
7.72 (1H, singlet),
10.32 (1H, broad singlet, disappeared on adding deuterium oxide),
13.1-13.7 (1H, broad, disappeared on adding deuterium oxide).

EXAMPLE 78

5-[2-(m-trifluoromethylanilino)thiazol-4-ylmethylene]rhodanine-3-acetic acid

The reaction described in Example 1 was repeated, but using 1 g of 2-(m-trifluoromethylanilino)thiazole-4-carbaldehyde, 0.7 g of rhodanine-3-acetic acid, 0.5 g of ammonium chloride, 0.5 ml of 28% v/v aqueous ammonia, and 10 ml of ethanol, to give the title compound as yellowish-orange prisms.
Melting point: 249 to 252 °C (with decomposition).
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
4.72 (2H, singlet),
7.37 (1H, broad doublet, J=8 Hz),
7. 58 (1H, broad triplet, J=8 Hz),
7.65 (1H, broad doublet, J=8 Hz),
7.69 (1H, singlet),
7.88 (1H, singlet),
8.43 (1H, broad singlet),
10.90 (1H, broad singlet, disappeared on adding deuterium oxide),
13.2-13.6 (1H, broad, disappeared on adding deuterium oxide.

EXAMPLE 79

5-(2-Ethylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid

The reaction described in Example 1 was repeated, but using 1.27 g of 2-ethylaminothiazole-4-carbaldehyde, 1.3 g of rhodanine-3-acetic acid, 1 g of ammonium chloride, 1 ml of 28% v/v aqueous ammonia and 30 ml of ethanol, to give 1.9 g of the title compound as yellow needles.
Melting point: 248 to 250 °C (with decomposition).
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.23 (3H, triplet, J=7 Hz),
3.3-3.45 (2H, multiplet),
4.70 (2H, singlet),
7.52 (1H, singlet),
7.54 (1H, singlet),
8.05 (1H, broad triplet, J=5 Hz),
13.33 (1H, broad singlet).

EXAMPLE 80

5-(2-Allylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid

The reaction described in Example 1 was repeated, but using 3.0 g of 2-allylaminothiazole-4-carbaldehyde, 2.8 g of rhodanine-3-acetic acid, 2.1 g of ammonium chloride, 2.1 ml of 28% v/v aqueous ammonia and 70 ml of ethanol, to give 3.3 g of the title compound as brown needles.

Melting point: 234 to 236 °C (with decomposition).
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
3.98-4.03 (2H, multiplet),
4.70 (2H, singlet),
5.16 (1H, doublet of doublets of doublets, J=10, 3 and 1.5 Hz),
5.29 (1H, doublet of doublets of doublets, J=17, 3, and 1.5 Hz),
5.90-6.05 (1H, multiplet),
7.54 (2H, singlet),
8.23 (1H, broad triplet, J=5 Hz),
13.1-13.6 (1H, broad).

EXAMPLE 81

5-(2-Cyclohexylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid

The reaction described in Example 1 was repeated, but using 3.0 g of 2-cyclohexylaminothiazole-4-carbaldehyde, 2.27 g of rhodanine-3-acetic acid, 1.7 g of ammonium chloride, 1.7 ml of 28% v/v aqueous ammonia and 60 ml of ethanol, to give the title compound as yellowish-brown needles.
Melting point: 220 to 222 °C (with decomposition).
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.15-1.5 (5H, multiplet),
1.55-1.85 (3H, multiplet),
2.0-2.1 (2H, multiplet),
3.55-3.7 (1H, multiplet),
4.70 (2H, singlet),
7.49 (1H, singlet),
7.52 (1H, singlet),
8.02 (1H, doublet, J=7 Hz, disappeared on adding deuterium oxide),
13.2-13.45 (1H, broad disappeared on adding deuterium oxide).

EXAMPLE 82

5-(2-Diphenylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid

The reaction described in Example 1 was repeated, but using 3 g of 2-diphenylaminothiazole-4-carbaldehyde, 1.7 g of rhodanine-3-acetic acid, 1.3 g of ammonium chloride, 1.3 ml of 28% v/v aqueous ammonia and 60 ml of ethanol, to give the title compound as orange needles.
Melting point: circa 305 to 310 °C (with decomposition).
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
4.69 (2H, singlet),
7.3-7.48 (2H, multiplet),
7.49 (4H, broad singlet),
7.51 (4H, broad singlet),
7.64 (1H, singlet),
7.75 (1H, singlet),
13.1-13.5 (1H, broad).

EXAMPLE 83

5-(2-Morpholinothiazol-4-ylmethylene)rhodanine-3-acetic acid

The reaction described in Example 1 was repeated, but using 1.65 g of 2-morpholinothiazole-4-carbaldehyde, 1.3 g of rhodanine-3-acetic acid, 1 g of ammonium chloride, 1 ml of 28% v/v aqueous ammonia and 35 ml of ethanol, to give the title compound as yellow needles.
Melting point: 287 to 290 °C (with decomposition).
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:

3.50 (4H, broad triplet, J=5 Hz),
3.76 (4H, broad triplet, J=5 Hz),
4.70 (2H, singlet),
7.61 (1H, singlet),
7.72 (1H, singlet),
13.0-13.7 (1H, broad).

EXAMPLE 84

5-(2-Piperidinothiazol-4-ylmethylene)rhodanine-3-acetic acid

The reaction described in Example 1 was repeated, but using 1.8 g of 2-piperidinothiazole-4-carbaldehyde, 1.4 g of rhodanine-3-acetic acid, 1.0 g of ammonium chloride, 1 ml of 28% v/v aqueous ammonia and 40 ml of ethanol, to give the title compound as yellow needles.
Melting point: 277 to 280 °C (with decomposition).
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.64 (6H, broad singlet),
3.52 (4H, broad singlet),
4.70 (2H, singlet),
7.57 (1H, singlet),
7.65 (1H, singlet),
13.0-13.7 (1H, broad).

EXAMPLE 85

5-[2-(Thiomorpholin-4-yl)thiazol-4-ylmethylene]rhodanine-3-acetic acid

The reaction described in Example 1 was repeated, but using 0.85 g of 2-(thiomorpholin-4-yl)thiazole-4-carbaldehyde, 0.76 g of rhodanine-3-acetic acid, 0.4 g of ammonium chloride, 0.4 ml of 28% v/v aqueous ammonia and 30 ml of ethanol, to give the title compound as yellow crystals.
Melting point: 267 to 270 °C (with decomposition).
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
2.7-2.8 (4H, multiplet),
3.8-3.9 (4H, multiplet),
4.71 (2H, singlet),
7.59 (1H, singlet),
7.70 (1H, singlet),
13.0-13.6 (1H, broad).

EXAMPLE 86

5-[2-(3-Benzoylthioureido)thiazol-4-ylmethylene]rhodanine-3-acetic acid

2.6 g of benzoyl isothiocyanate were added dropwise, at room temperature to a solution of 4 g of 5-(2-aminothiazol-4-ylmethylene)rhodanine-3-acetic acid in 70 ml of dimethylformamide. The reaction mixture was stirred at room temperature for 6 hours, and then ethyl acetate was added and precipitated solids were filtered off. The ethyl acetate solution was washed with water and concentrated by evaporation under reduced pressure, and the crystalline solid thus obtained was separated by filtration and recrystallized from acetic acid, to give the title compound as a yellow powder.
Melting point: 248 to 250 °C (with decomposition).
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
4.73 (2H, singlet),
7.57 (2H, broad triplet, J=8 Hz),
7.71 (2H, broad triplet, J=8 Hz),
7.84 (1H, singlet),
8.06 (2H, broad doublet, J=8 Hz),

8.09 (1H, singlet),
12.27 (1H, singlet, disappeared on adding deuterium oxide),
13.0-13.7 (1H, broad, disappeared on adding deuterium oxide),
14.30 (1H, singlet, disappeared on adding deuterium oxide).

EXAMPLE 87

5-[2-(4-Methyl-1-piperazinyl)thiazol-4-ylmethylene]rhodanine-3-acetic acid

The reaction described in Example 1 was repeated, but using 1.8 g of 2-(4-methyl-1-piperazinyl)thiazole-4-carbaldehyde, 1.2 g of rhodanine-3-acetic acid, 0.9 g of ammonium chloride, 0.9 ml of 28% v/v aqueous ammonia, and 40 ml of ethanol, to give the title compound as dark yellow needles.
Melting point: over 300 °C.
Nuclear Magnetic Resonance Spectrum (CF_3COOD) δ ppm:
3.24 (3H, singlet),
3.63 (2H, broad doublet of triplets, J=13 and 3 Hz),
4.04 (2H, broad doublet, J=13 Hz),
4.22 (2H, broad triplet, J=13 Hz),
4.39 (2H, broad doublet, J=13 Hz),
5.11 (2H, singlet),
7.60 (1H, singlet).

EXAMPLE 88

5-(2-Octylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid 1/3 ethanol adduct

The reaction described in Example 1 was repeated, but using 1.1 g of 2-octylaminothiazole-4-carbaldehyde, 0.66 g of rhodanine-3-acetic acid, 0.5 g of ammonium chloride, 0.5 ml of 28% v/v aqueous ammonia and 30 ml of ethanol, to give the title compound as pale brown needles.
Melting point: 147 to 149 °C.
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
0.85 (3H, broad triplet, J=7 Hz),
1.06 (1H, triplet, J=7 Hz),
1.15-1.45 (10H, multiplet),
1.55-1.7 (2H, multiplet),
3.2-3.5 (2 .67H, not defined),
4.25-4.4 (0.33H, multiplet),
4.70 (2H, singlet),
7.50 (1H, singlet),
7.53 (1H, singlet),
8.06 (1H, triplet, J=5 Hz),
13.0-13.6 (1H, broad).

EXAMPLE 89

5-(2-Isopropylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid

The reaction described in Example 1 was repeated, but using 2.7 g of 2-isopropylaminothiazole-4-carbaldehyde, 2.3 g of rhodanine-3-acetic acid, 1.7 g of ammonium chloride, 1.7 ml of 28% v/v aqueous ammonia and 50 ml of ethanol, to give the title compound as dark red needles.
Melting point: 227 to 229 °C (with decomposition).
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.25 (6H, doublet, J=7 Hz),
3.85-4.0 (1H, multiplet),
4.70 (2H, singlet),
7.51 (1H, singlet),

7.53 (1H, singlet),
7.98 (1H, doublet, J=7 Hz),
13.0-13.8 (1H, broad).

EXAMPLE 90

5-(2-Benzylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid

The reaction described in Example 1 was repeated, but using 0.58 g of 2-benzylaminothiazole-4-carbaldehyde, 0.5 g of rhodanine-3-acetic acid, 0.3 g of ammonium chloride, 0.3 ml of 28% v/v aqueous ammonia and 40 ml of ethanol, to give the title compound as yellow needles.
Melting point: 207 to 210 °C.
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
4.58 (2H, doublet, J=6 Hz),
4.69 (2H, singlet),
7.2 - 7.45 (5H, multiplet),
7.53 (2H, singlet),
8.57 (1H, triplet, J=6 Hz, disappeared on adding deuterium oxide),
13.0-13.6 (1H, broad, disappeared on adding deuterium oxide),

EXAMPLE 91

5-{1-[2-(3-Benzoylthioureido)thiazol-4-yl]-1-carboxymethylene}rhodanine-3-acetic acid monohydrate

The reaction described in Example 1 was repeated, but using 1.0 g of crude sodium 2-(3-benzoylthioureido)thiazol-4-ylglyoxylate, 0.75 g of rhodanine-3-acetic acid, 0.2 g of ammonium chloride, 0.5 ml of 28% v/v aqueous ammonia and 20 ml of ethanol, to give the title compound as a yellow powder.
Melting point: 255 to 265 °C.
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
4.71 (2H, singlet),
7.58 (2H, broad triplet, J=8 Hz),
7.71 (1H, broad triplet, J=8 Hz),
7.77 (1H, singlet),
8.06 (2H, broad doublet, J=8 Hz),
12.3 (1H, broad singlet, disappeared on adding deuterium oxide),
13.0-13.9 (1H, broad, disappeared on adding deuterium oxide),
13.9-14.7 (2H, broad, disappeared on adding deuterium oxide).

EXAMPLE 92

5-(2-Cyclopropylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid

The reaction described in Example 1 was repeated, but using 0.53 g of 2-cyclopropylaminothiazole-4-carbaldehyde, 0.46 g of rhodanine-3-acetic acid, 0.3 g of ammonium chloride, 0.3 ml of 28% v/v aqueous ammonia and 20 ml of ethanol, to give the title compound as an orange powder.
Melting point: 255 to 257 °C.
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
0.54-0.6 (2H, multiplet),
0.74-0.81 (2H, multiplet),
2.6-2.7 (1H, multiplet),
4.69 (2H, singlet),
7.56 (1H, singlet),
7.58 (1H, singlet),
8.38 (1H, doublet, J=1 Hz),
13.1-13.6 (1H, broad).

PREPARATION 1

Ethyl 2-(3-phenylureido)thiazol-4-ylglyoxylate

10 g of ethyl 2-aminothiazol-4-ylglyoxylate were dissolved in 100 ml of dimethylformamide, and 7.14 g of phenyl isocyanate were added dropwise to the resulting solution under ice-cooling. The mixture was left to stand overnight, and the dimethylformamide was then evaporated off under reduced pressure. The crystals thus obtained were washed with water, dried and recrystallized from ethyl acetate, to give the desired compound as yellow crystals.

Melting point: 217 to 220 °C

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J = 7 Hz),
4.38 (2H, quartet, J = 7 Hz),
6.95-7.6 (5H, multiplet),
8.41 (1H, singlet),
8.93 (1H, broad singlet),
10.8-11.3 (1H, broad singlet).

PREPARATION 2

Ethyl 2-(3-o-methoxyphenylureido)thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 5 g of ethyl 2-aminothiazol-4-ylglyoxylate, 4.5 g of o-methoxyphenyl isocyanate and 40 ml of dimethylformamide. The resulting product was a yellow powder having the following physical properties.

Melting point: 223 to 227 °C

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J = 7 Hz),
3.88 (3H, singlet),
4.38 (2H, quartet, J = 7 Hz),
6.9-7.0 (1H, multiplet),
7.0-7.1 (2H, multiplet),
8.05-8.15 (1H, multiplet),
8.39 (1H, singlet),
8.65 (1H, broad singlet, disappeared on adding deuterium oxide),
11.46 (1H, broad singlet, disappeared on adding deuterium oxide).

PREPARATION 3

Ethyl 2-(3-m-methoxyphenylureido)thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 5 g of ethyl 2-aminothiazol-4-ylglyoxylate, 4.5 g of methoxyphenyl isocyanate and 40 ml of dimethylformamide, as yellow crystals having the following physical properties.

Melting point: 182 to 185 °C

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.33 (3H, triplet, J = 7 Hz),
3.75 (3H, singlet),
4.37 (2H, quartet, J = 7 Hz),
6.64 (1H, doublet of doublets, J = 2 and 8 Hz),
6.95-7.0 (1H, multiplet),
7.16 (1H, triplet, J = 2 Hz),
7.23 (1H, triplet, J = 8 Hz),
8.41 (1H, singlet),
8.90 (1H, broad singlet, disappeared on adding deuterium oxide),
10.99 (1H, broad singlet, disappeared on adding deuterium oxide).

European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 89303751.5

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	FR - A1 - 2 117 337 (EASTMAN KODAK COMPANY) * Claim 2; page 2, lines 5-14 *	1,10, 12	C 07 D 277/38 A 61 K 31/425
A	CHEMICAL ABSTRACTS, vol. 85, no. 3, July 19, 1976, Columbus, Ohio, USA ACHARY, T.E.; DHAL, P. N.; NAYAK, A. "Studies on thiazolidinones: Part IV. Thiazolidinones and their derivatives from unsymmetrical thioureas" page 676, column 1, abstract-no. 21 190g & J. Indian Chem. Soc. 1975, 52(12), 1204-6	1,10,	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 D 277/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	22-06-1989	BRUS

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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PREPARATION 4

Ethyl 2-(3-p-methoxyphenylureido)thiazol-4-ylglyoxylate

Following the procedures described in Preparation 1, the desired compound was prepared using 10 g of ethyl 2-aminothiazol-4-ylglyoxylate, 9 g of p-methoxyphenyl isocyanate and 80 ml of dimethylformamide as yellow powders. The product has the following physical properties.
Melting point: 193 to 196 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.33 (3H, triplet, J = 7 Hz),
3.73 (3H, singlet),
4.37 (2H, quartet, J = 7 Hz),
6.90 (2H, doublet, J = 9 Hz),
7.38 (2H, doublet, J = 9 Hz),
8.39 (1H, singlet),
8.72 (1H, broad singlet, disappeared on adding deuterium oxide),
10.96 (1H, broad singlet, disappeared on adding deuterium oxide).

PREPARATION 5

Ethyl 2-(3-p-fluorophenylureido)thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 5 g of ethyl 2-aminothiazol-4-ylglyoxylate, 5.1 g of p-fluorophenyl isocyanate and 30 ml of dimethylformamide. The resulting product was a yellow powder having the following physical properties.
Melting point: 220 to 223 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J = 7 Hz),
4.39 (2H, quartet, J = 7 Hz),
7.17 (2H, triplet, J = 9 Hz),
7.53 (2H, doublet of doublets, J = 5 and 9 Hz),
8.43 (1H, singlet),
8.96 (1H, broad singlet),
11.09 (1H, broad singlet).

PREPARATION 6

Ethyl 2-(3-p-chlorophenylureido)thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 10 g of ethyl 2-aminothiazol-4-ylglyoxylate, 8.6 g of p-chlorophenyl isocyanate and 100 ml of dimethylformamide. The resulting product was a yellow powder having the following physical properties.
Melting point: 230 to 234 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J = 7 Hz),
4.39 (2H, quartet, J = 7 Hz),
7.38 (2H, doublet, J = 9 Hz),
7.55 (2H, doublet, J = 9 Hz),
8.43 (1H, singlet),
9.06 (1H, broad singlet),
11.14 (1H, broad singlet).

PREPARATION 7

Ethyl 2-(3-p-bromophenylureido)thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 10 g of ethyl 2-aminothiazol-4-ylglyoxylate, 8.7 g of p-bromophenyl isocyanate and 80 ml of dimethylformamide, as yellow crystals having the following physical properties.
Melting point: 235 to 241 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.33 (3H, triplet, J = 7 Hz),
4.37 (2H, quartet, J = 7 Hz),
7.44-7.53 (4H, multiplet),
8.42 (1H, singlet),
9.05 (1H, broad singlet),
11.10 (1H, broad singlet),

PREPARATION 8

Ethyl 2-[3-(3,4-dichlorophenyl)ureido]thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 10 g of ethyl 2-aminothiazol-4-ylglyoxylate, 10 g of 3,4-dichlorophenyl isocyanate and 100 ml of dimethylformamide. The resulting product was a pale yellow powder having the following physical properties.
Melting point: circa 250 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J = 7 Hz),
4.39 (2H, quartet, J = 7 Hz),
7.43 (1H, doublet of doublets, J = 2 and 9 Hz),
7.59 (1H, doublet, J = 9 Hz),
7.89 (1H, doublet, J = 2 Hz),
8.46 (1H, singlet),
9.22 (1H, broad singlet),
11.29 (1H, broad singlet).

PREPARATION 9

Ethyl 2-[3-(1-naphthyl)ureido]thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 10 g of ethyl 2-aminothiazol-4-ylglyoxylate, 10.1 g of 1-naphthyl isocyanate and 100 ml of dimethylformamide. The resulting product was a grayish-white powder having the following physical properties.
Melting point: 209 to 211 °C
Nuclear Magnetic Resonance Spectrum (heptadeuterated dimethylformamide) δ ppm:
1.37 (3H, triplet, J = 7 Hz),
4.44 (2H, quartet, J = 7 Hz),
7.45-8.4 (7H, multiplet),
8.47 (1H, singlet),
9.44 (1H, broad singlet),
10.8-11.7 (1H, broad singlet),

PREPARATION 10

Ethyl 2-(3-p-toluenesulphonylureido)thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 6 g of ethyl 2-aminothiazole-4-ylglyoxylate, 6 g of p-toluenesulphonyl isocyanate and 40 ml of

dimethylformamide. The resulting product was a pale yellow powder having the following physical properties.
Melting point: 200 to 207 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.31 (3H, triplet, J = 7 Hz),
2.40 (3H, singlet),
4.35 (2H, quartet, J = 7 Hz),
7.44 (2H, doublet, J = 8 Hz),
7.86 (2H, doublet, J = 8 Hz),
8.44 (1H, singlet),
11.10-11.65 (1H, broad singlet).

PREPARATION 11

Ethyl 2-(3-phenylthioureido) thiazol-4-ylglyoxylate

5 g of ethyl 2-aminothiazol-4-ylglyoxylate were dissolved in 30 ml of hexamethylphosphoric triamide, and 5.2 g of phenyl isothiocyanate were added to the resulting solution under ice-cooling. The reaction mixture was kept stirred at an external temperature of 60 °C for 8 hours, and then acidified with dilute hydrochloric acid and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulphate and then concentrated by evaporation under reduced pressure. The crystals which precipitated out were collected by filtration to give the desired compound as pale yellow crystals.
Melting point: 190 to 192 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.33 (3H, triplet, J = 7 Hz),
4.41 (2H, quartet, J = 7 Hz),
7.10-7.77 (5H, multiplet),
8.40 (1H, singlet),
10.52 (1H, broad singlet),
11.8-12.6 (1H, broad).

PREPARATION 12

Ethyl 2-(3-p-chlorophenylthioureido)thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 5 g of ethyl 2-aminothiazol 4-ylglyoxylate, 6.35 g of p-chlorophenyl isothiocyanate and 30 ml of hexamethylphosphoric triamide. The resulting product was a yellow powder having the following physical properties.
Melting point: 176 to 178 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (heptadeuterated dimethylformamide) δ ppm:
1.35 (3H, triplet, J = 7 Hz),
4.43 (2H, quartet, J = 7 Hz),
7.45 (2H, broad doublet, J = 9 Hz),
7.80 (2H, broad doublet, J = 9 Hz),
8.43 (1H, singlet),
10.7-11.2 (1H, broad).

PREPARATION 13

Ethyl 2-benzamidothiazol-4-ylglyoxylate

5 g of ethyl 2-aminothiazol-4-ylglyoxylate were dissolved in 50 ml of tetrahydrofuran, and 5.55 g of benzoyl bromide were added dropwise to the resulting solution under ice-cooling. The reaction mixture was kept stirred for one hour, and then water was added to it, in order to precipitate out crystals. The crystals were collected by filtration and purified by silica gel column chromatography, using as eluent a 2:1 by volume mixture of hexane and ethyl acetate. The resulting product was a white powder having the following physical

properties.
Melting point: 152 to 153 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm:
1.40 (3H, triplet, J = 7 Hz),
4.44 (2H, quartet, J = 7 Hz),
7.43-7.73 (2H, multiplet),
8.10-8.36 (2H, multiplet),
8.37 (1H, singlet).

PREPARATION 14

Ethyl 2-tritylaminothiazole-4-carboxylate

A mixture comprising 5 g of triphenylchloromethane and 15 ml of dichloromethane was added dropwise at -30 °C to a mixture comprising 3.1 g of ethyl 2-aminothiazole-4-carboxylate, 25 ml of dimethylformamide and 1.8 g of triethylamine. The reaction mixture was maintained at -30 °C for 10 minutes and was then stirred at room temperature for 2 hours, after which it was poured into ice water and extracted with ethyl acetate. The extract was washed successively with 0.1N hydrochloric acid and an aqueous sodium chloride solution, and then dried over anhydrous sodium sulphate. The solvent was evaporated off under reduced pressure, and the residue was purified by silica gel chromatography, using as eluent a 10:1 by volume mixture of benzene and ethyl acetate. The crystals obtained thereby were washed with n-hexane, to afford the desired compound as a white powder.
Melting point: 14o to 141 °C

PREPARATION 15

2-Tritylaminothiazole-4-methanol

A mixture comprising 2.6 g of ethyl 2-tritylaminothiazole-4-carboxylate and 10 ml of tetrahydrofuran was added dropwise under ice-cooling to a mixture comprising 0.24 g of lithium aluminium hydride and 30 ml of tetrahydrofuran, under a stream of nitrogen. After completion of the dropwise addition, the resulting mixture was stirred at room temperature for 3 hours, and then with heating under reflux for one hour. Ethyl acetate and then water were added to the reaction mixture under ice-cooling, the organic layer was separated off, and the aqueous layer was re-extracted with ethyl acetate. The combined ethyl acetate extract was washed with a saturated aqueous sodium chloride solution, and then dried over anhydrous sodium sulphate. The solvent was evaporated off under reduced pressure, and the residue was purified by silica gel column chromatography, using as eluent a 1:1 by volume mixture of benzene and ethyl acetate. The product was recrystallized from a mixture of ethyl acetate, acetone and n-hexane, to give the desired compound as a pale yellow powder.
Melting point: 186 to 187 °C

PREPARATION 16

2-Tritylaminothiazole-4-carbaldehyde

A mixture comprising 0.5 g of 2-tritylaminothiazole- 4-methanol, 5 g of manganese dioxide and 20 ml of acetone was stirred at room temperature for 60 hours. The manganese dioxide was then filtered off and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography, using as eluent a 10:1 by volume mixture of benzene and ethyl acetate, to give the desired compound as a brownish-orange powder.
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
7.19-7.36 (15H, multiplet),
7.70 (1H, broad singlet),
8.93 (1H, broad singlet, disappeared on adding deuterium oxide),
9.40 (1H, singlet),
Mass spectrum (m/e) : 370 (M^+)

PREPARATION 17

4-(1,2-Dihydroxyethyl)-2-(3-phenylureido)thiazole

7 ml of methanol were added dropwise, over a period of one hour, to a mixture comprising 1 g of ethyl 2-(3-phenylureido)thiazol-4-ylglyoxylate, 0.6 g of sodium borohydride and 20 ml of tetrahydrofuran kept heated under reflux. The resulting mixture was cooled to room temperature and acidified with 3N hydrochloric acid. The solvent was evaporated off under reduced pressure, and the residue was washed with water, to give the desired compound as a white powder.
Melting point: 175 to 178 °C

PREPARATION 18

2-(3-phenylureido)thiazole-4-carbaldehyde

A solution of 0.76 g of sodium metaperiodate in 15 ml of water was added dropwise at room temperature to a mixture comprising 0.5 g of 4-(1,2-dihydroxyethyl)-2-(3-phenylureido) thiazole and 15 ml of methanol, and the mixture was stirred for 2 hours after completion of the dropwise addition. The solvent was then evaporated off under reduced pressure and the residue was washed with water, to give the desired compound as a white powder.
Melting point: 216 to 220 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
6.9-7.7 (5H, multiplet),
8.26 (1H, singlet),
9.03 (1H, broad singlet),
9.83 (1H, singlet),
10.5-11.2 (1H, broad).

PREPARATION 19

Ethyl 2-(3-benzoylthioureido)thiazol-4-ylglyoxylate

The reaction described in Preparation 1 was repeated, but using 20 g of ethyl 2-aminothiazol-4-yl-glyoxylate 16.5 g of benzoyl isothiocyanate, and 100 ml of dimethylformamide, to give the title compound as a pale yellow powder.
Melting point: 155 to 157 °C.
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J=7 Hz),
4.40 (2H, quartet, J=7 Hz),
7.57 (2H, triplet, J=8 Hz),
7.70 (1H, triplet, J=8 Hz),
8.01 (2H, doublet, J=8 Hz),
8.53 (1H, singlet),
12.1-12.5 (1H, broad, disappeared on adding deuterium oxide),
14.0-14.4 (1H, broad, disappeared on adding deuterium oxide).

PREPARATION 20

Isobutyl 2-aminothiazol-4-ylglyoxylate

A mixture comprising 10 g of potassium 2-aminothiazol-4-ylglyoxylate, 15 g of isobutyl alcohol and 50 ml of a 4N dioxane solution of hydrogen chloride was stirred at room temperature for 2 days. At the end of this time, the reaction mixture was poured into water and neutralized with potassium carbonate, followed by extraction

with ethyl acetate. The extract was dried over anhydrous magnesium sulphate and the ethyl acetate was evaporated off under reduced pressure, to give the desired compound as a pale yellow powder.
Melting point: 105 to 108 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
0.93 (6H, doublet, J = 7 Hz),
1.98 (1H, septet, J = 7 Hz),
4.08 (2H, doublet, J = 7 Hz),
7.40 (2H, broad singlet),
7.89 (1H, singlet).

PREPARATION 21

Isobutyl 2-(3-phenylureido)thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 1 g of isobutyl 2-aminothiazol-4-ylglyoxylate, 620 mg of phenyl isocyanate and 10 ml of tetrahydrofuran. The resulting product was a pale yellow powder having the following physical properties.
Melting point: 190 to 200 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
0.96 (6H, doublet, J = 7 H,),
2.02 (1H, septet, J = 7 Hz),
4.14 (2H, doublet, J = 7 Hz),
7.06 (1H, triplet, J = 7 Hz),
7.33 (2H, triplet, J = 8 Hz),
7.48 (2H, doublet, J = 7 Hz),
8.40 (1H, singlet),
8.92 (1H, broad singlet),
10.98 (1H, broad singlet).

PREPARATION 22

Ethyl 2-(3-o-fluorophenylureido)thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 5 g of ethyl 2-aminothiazol-4-ylglyoxylate, 4.87 g of o-fluorophenyl isocyanate and 30 ml of dimethylformamide. The resulting product was a pale yellow powder having the following physical properties.
Melting point: 219 to 225 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.34 (3H, triplet, J = 7 Hz),
4.38 (2H, quartet, J = 7 Hz),
7.1-7.15 (1H, multiplet),
7.20 (1H, triplet, J = 8 Hz),
7.29 (1H, doublet of doublets, J = 11 and 8 Hz),
8.08 (1H, triplet, J = 8 Hz),
8.43 (1H, singlet),
8.85 (1H, broad singlet, disappeared on adding deuterium oxide),
11.22 (1H, broad singlet, disappeared on adding deuterium oxide).

PREPARATION 23

Ethyl 2-(3-m-fluorophenylureido)thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 5 g of ethyl 2-aminothiazol-4-ylglyoxylate, 4.9 g of m-fluorophenyl isocyanate and 30 ml of dimethylformamide. The resulting product was a pale yellow powder having the following physical properties.
Melting point: 215 to 216 °C

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.33 (3H, triplet, J = 7 Hz),
4.38 (2H, quartet, J = 7 Hz),
6.89 (1H, doublet of triplets, J = 2 and 8 Hz),
7.20 (1H, doublet of triplets, J = 8 and 1 Hz),
7.36 (1H, doublet of triplets, J = 7 and 8 Hz),
7.47 (1H, doublet of triplets, J = 12 and 2 Hz),
8.43 (1H, singlet),
9.13 (1H, broad singlet),
11.13 (1H, broad singlet).

PREPARATION 24

Ethyl 2-[3-(2,4-difluorophenyl)ureido]thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 5 g of ethyl 2-aminothiazol-4-ylglyoxylate, 5.8 g of 2,4-difluorophenyl isocyanate and 30 ml of dimethylformamide. The resulting product was a white powder having the following physical properties.
Melting point: 245 to 263 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.33 (3H, triplet, J = 7 Hz),
4.38 (2H, quartet, J = 7 Hz),
7.05-7.15 (1H, multiplet),
7.35 (1H, doublet of doublets of doublets, J = 11, 9 and 3 Hz),
8.00 (1H, doublet of triplets, J = 6 and 9 Hz),
8.42 (1H, singlet),
8.79 (1H, broad singlet),
11.22 (1H, broad singlet).

PREPARATION 25

Ethyl 2-[3-(4-fluoro-3-nitrophenyl)ureido]thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 5 g of ethyl 2-aminothiazol-4-ylglyoxylate, 5.5 g of 4-fluoro-3-nitrophenyl isocyanate and 30 ml of dimethylformamide. The resulting product was a yellow powder having the following physical properties.
Melting point: 230 to 240 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.33 (3H, triplet, J = 7 Hz),
4.38 (2H, quartet, J = 7 Hz),
7.56 (1H, doublet of doublets, J = 11 and 9 Hz),
7.76-7.85 (1H, multiplet),
8.42 (1H, doublet of doublets, J = 6 and 3 Hz),
8.46 (1H, singlet),
9.40 (1H, broad singlet, disappeared on adding deuterium oxide),
11.42 (1H, broad singlet, disappeared on adding deuterium oxide).

PREPARATION 26

Ethyl 2-dimethylaminothiazol-4-ylglyoxylate

A mixture comprising 10 ml of a 2M benzene solution of dimethylamine, 1.3 g of ethyl 2-chlorothiazol-4-ylglyoxylate, and 5 ml of tetrahydrofuran was stirred for 3 hours at room temperature. At the end of this time, the reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulphate, and concentrated by evaporation under reduced pressure. The residue was purified by silica gel column chromatography, using as eluent a 9:1 by volume mixture of

benzene and ethyl acetate, to give the title compound as a pale yellow oil.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.40 (3H, triplet, J=7 Hz),
2.16 (6H, singlet),
4.41 (2H, quartet, J=7 Hz),
7.83 (1H, singlet),

PREPARATION 27

Ethyl 2-[3-(3,4,5-trimethoxyphenyl)ureido]thiazol-4-yl-glyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 4.3 g of ethyl 2-aminothiazol-4-ylglyoxylate, 5 g of 3,4,5-trimethoxyphenyl isocyanate and 30 ml of dimethylformamide. The resulting product was a yellow powder having the following physical properties.
Melting point: 185 to 186 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.33 (3H, triplet, J = 7 Hz),
3.62 (3H, singlet),
3.77 (6H, singlet),
4.37 (2H, quartet, J = 7 Hz),
6.82 (2H, singlet),
8.41 (1H, singlet),
8.88 (1H, broad singlet, disappeared on adding deuterium oxide),
10.9-11.3 (1H, broad, disappeared on adding deuterium oxide).

PREPARATION 28

Ethyl 2-(3-o-chlorophenylureido)thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 26.7 g of ethyl 2-aminothiazol-4-ylglyoxylate, 23 g of o-chlorophenyl isocyanate and 300 ml of dimethylformamide. The resulting product was a white powder having the following physical properties.
Melting point: 246 to 248 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.33 (3H, triplet, J = 7 Hz),
4.38 (2H, quartet, J = 7 Hz),
7.13 (1H, doublet of triplets, J = 1.5 and 8 Hz),
7.35 (1H, doublet of triplets, J = 1.5 and 8 Hz),
7.51 (1H, doublet of doublets, J = 8 and 1.5 Hz),
8.13 (1H, doublet of doublets, J = 8 and 1.5 Hz),
8.44 (1H, singlet),
8.66 (1H, broad singlet),
11. 66 (1H, broad singlet).

PREPARATION 29

Ethyl 2-(3-p-tolylureido)thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 12 g of ethyl 2-aminothiazol-4-ylglyoxylate, 10 g of p-tolyl isocyanate and 80 ml of dimethylformamide. The resulting product was a yellow powder having the following physical properties.
Melting point: 210 to 212 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.33 (3H, triplet, J = 7 Hz),
2.26 (3H, singlet),
4.37 (2H, quartet, J = 7 Hz),

7.13 (2H, doublet, J = 9 Hz),
7.36 (2H, doublet, J = 9 Hz),
8.40 (1H, singlet),
8.79 (1H, broad singlet),
10.97 (1H, broad singlet).

PREPARATION 30

Ethyl 2-[3-(2,6-xylyl)ureido]thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 5 g of ethyl 2-aminothiazol-4-ylglyoxylate, 5.5 g of 2,6-xylyl isocyanate and 30 ml of dimethylformamide. The resulting product was a pale yellow powder having the following physical properties.
Melting point: 172 to 174 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.33 (3H, triplet, J = 7 Hz),
2.19 (6H, singlet),
4.37 (2H, quartet, J = 7 Hz),
7.10 (3H, singlet),
8.09 (1H, broad singlet),
8.35 (1H, singlet),
11.21 (1H, broad singlet).

PREPARATION 31

Ethyl 2-(3-p-nitrophenylureido)thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 4.88 g of ethyl 2-aminothiazol-4-ylglyoxylate, 5 g of p-nitrophenyl isocyanate and 30 ml of dimethylformamide. The resulting product was a pale yellow powder having the following physical properties.
Melting point: 243 to 265 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.33 (3H, triplet, J = 7 Hz),
4.38 (2H, quartet, J = 7 Hz),
7.75 (2H, doublet, J = 9 Hz),
8.23 (2H, doublet, J = 9 Hz),
8. 47 (1H, singlet),
9.61 (1H, broad singlet),
11.33 (1H, broad singlet).

PREPARATION 32

Ethyl 2-(3-o-trifluoromethylphenylureido)thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 4.28 g of ethyl 2-aminothiazol-4-ylglyoxylate, 5 g of o-trifluoromethylphenyl isocyanate and 40 ml of dimethylformamide. The resulting product was a white powder having the following physical properties.
Melting point: circa 260 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.33 (3H, triplet, J = 7 Hz),
4.37 (2H, quartet, J = 7 Hz),
7.38 (1H, broad triplet, J = 8 Hz),
7.69-7.75 (2H, not defined),
7.94 (1H, broad doublet, J = 8 Hz),
8.41 (1H, broad singlet),
8.42 (1H, singlet),

11.65 (1H, broad singlet).

PREPARATION 33

Ethyl 2-(3-p-trifluoromethylphenylureido)thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 4.28 g of ethyl 2-aminothiazol-4-ylglyoxylate, 5 g of p-trifluoromethylphenyl isocyanate and 40 ml of dimethylformamide. The resulting product was a pale yellow powder having the following physical properties.
Melting point: 240 to 245 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.33 (3H, triplet, J = 7 Hz),
4.38 (2H, quartet, J = 7 Hz),
7.69 and 7.70 (4H, A_2B_2, J = 10 Hz),
8.45 (1H, singlet),
9.31 (1H, broad singlet),
11.20 (1H, broad singlet).

PREPARATION 34

Ethyl 2-(3,3-diphenylureido)thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 13, the desired compound was prepared from 5 g of ethyl 2-aminothiazol-4-ylglyoxylate, 7 g of diphenylcarbamoyl chloride, 30 ml of triethylamine and 20 ml of dimethylformamide. The resulting product was a brown oil having the following physical properties.
Nuclear Magnetic Resonance Spectrum ($CDC\ell_3$) δ ppm:
1.38 (3H, triplet, J = 7 Hz),
4.39 (2H, quartet, J = 7 Hz),
7.2-7.5 (10H, multiplet),
8.27 (1H, singlet).

PREPARATION 35

Ethyl 2-(3-methylureido)thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 10 g of ethyl 2-aminothiazol-4-ylglyoxylate, 7 g of methyl isocyanate and 200 ml of ethyl acetate. The resulting product was a pale yellow powder having the following physical properties.
Melting point: 210 to 213 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.32 (3H, triplet, J = 7 Hz),
2.71 (3H, doublet, J = 4 Hz),
4.37 (2H, quartet, J = 7 Hz),
6.41 (1H, broad quartet, J = 4 Hz, disappeared on adding deuterium oxide),
8.31 (1H, singlet),
11.08 (1H, broad singlet, disappeared on adding deuterium oxide).

PREPARATION 36

Ethyl 2-(3-benzylureido)thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 4.7 g of ethyl 2-aminothiazol-4-ylglyoxylate, 4.5 g of benzyl isocyanate and 30 ml of dimethylformamide. The

resulting product was a yellow powder having the following physical properties.
Melting point: circa 218 °C (with decomposition)
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.32 (3H, triplet, J = 7 Hz),
4.36 (2H, quartet, J = 7 Hz),
4.37 (2H, singlet),
7.03 (1H, broad triplet, J = 6 Hz),
7.2-7.4 (5H, multiplet),
8.33 (1H, singlet),
11.08 (1H, broad singlet, disappeared on adding deuterium oxide).

PREPARATION 37

Ethyl 2-(3-cyclohexylureido)thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 5 g of ethyl 2-aminothiazol-4-ylglyoxylate, 4.7 g of cyclohexyl isocyanate and 30 ml of dimethylformamide. The resulting product was a yellow powder having the following physical properties.
Melting point: 212 to 215 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.1-1.4 (5H, not defined),
1.32 (3H, triplet, J = 7 Hz),
1.5-1.6 (1H, multiplet),
1.6-1.75 (2H, multiplet),
1.75-1.9 (2H, multiplet),
3.45-3.6 (1H, multiplet),
4.35 (2H, quartet, J = 7 Hz),
6.44 (1H, broad doublet, J = 8 Hz),
8.31 (1H, singlet),
10.64 (1H, broad singlet).

PREPARATION 38

Ethyl 2-[3-(2,4,6-trifluorophenyl)ureido]thiazol-4-ylglyoxylate

A mixture comprising 25 g of carbonyldiimidazole, 30.87 g of ethyl 2-aminothiazol-4-ylglyoxylate and 300 ml of tetrahydrofuran was stirred at room temperature for 1 day. After completion of the reaction, the crystals which precipitated out were collected by filtration and washed with ethyl acetate to give crude ethyl 2-(1-imidazolylcarbonylamino)thiazol-4-ylglyoxylate.

A mixture comprising 7.92 g of this crude intermediate, 5 g of 2,4,6-trifluoroaniline and 100 ml of dimethylformamide was stirred overnight at room temperature. The reaction mixture was then concentrated by evaporation under reduced pressure and then ethyl acetate was added. Insolubles were filtered off, and the filtrate was purified by silica gel column chromatography, using as eluent a 8:2:1 to 6:2:1 mixture of hexane, ethyl acetate and acetic acid.

The resulting product was a white powder having the following physical properties.
Melting point: 242 to 248 °C (with decomposition).
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.32 (3H, triplet, J=7 Hz),
4.37 (2H, quartet, J=7 Hz),
7.31 (2H, doublet of doublets, J=9 and 8 Hz),
8.41 (1H, singlet),
8.42 (1H, singlet, disappeared on adding deuterium oxide),
11.60 (1H, broad singlet, disappeared on adding deuterium oxide).

PREPARATION 39

2-Diethylaminothiazole-4-carbaldehyde

The reaction described in Preparation 26 was repeated, but using 2.3 g of diethylamine, 4 g of ethyl 2-chlorothiazole-4-carboxylate, 4.2 g of triethylamine, and 15 ml of dimethylformamide, to give ethyl 2-diethylaminothiazole-4-carboxylate as a pale yellow oil.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.24 (6H, triplet, J=7 Hz),
1.37 (3H, triplet, J=7 Hz),
3.53 (4H, quartet, J=7 Hz),
4.34 (2H, quartet, J=7 Hz),
7.36 (1H, singlet).

The reaction described in Preparation 15 was then repeated, but using 1.9 g of the above ester, 0.31 g of lithium aluminium hydride, and 40 ml of tetrahydrofuran, to give 2-diethylaminothiazol-4-ylmethanol as colourless prisms.

Melting point: 67 to 69 °C.

A dimethyl sulphoxide (10 ml) solution of 3.3 g of pyridine sulphur trioxide complex was added dropwise, with stirring and at room temperature, to a mixture comprising 1.3 g of the above methanol derivative, 2.1 g of triethylamine and 10 ml of dimethyl sulphoxide. The reaction mixture was stirred for 30 minutes at the same temperature, and then poured into water and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulphate and concentrated by evaporation under reduced pressure. The residue was purified by silica gel column chromatography, using as eluent a 5:1 by volume mixture of benzene and ethyl acetate, to give the title compound as a pale brown oil.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.26 (6H, triplet, J=7 Hz),
3.54 (4H, quartet, J=7 Hz),
7.39 (1H, singlet),
9.74 (1H, singlet).

PREPARATION 40

Ethyl 2-(3-o-fluorophenylthioureido)thiazol-4-yl-glyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 15 g of ethyl 2-aminothiazol-4-ylglyoxylate, 17 g of o-fluorophenyl isothiocyanate and 30 ml of hexamethylphosphoric triamide. The resulting product was a pale yellow powder having the following physical properties.

Melting point: 192 to 193 °C

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.32 (3H, triplet, J = 7 Hz),
4.37 (2H, quartet, J = 7 Hz),
7.2-7.35 (3H, multiplet),
7.79 (1H, triplet, J = 8 Hz),
8.39 (1H, singlet),
10.12 (1H, broad singlet, disappeared on adding deuterium oxide),
12.45 (1H, broad singlet, disappeared on adding deuterium oxide).

PREPARATION 41

Ethyl 2-(3-p-fluorophenylthioureido)thiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 1, the desired compound was prepared from 5 g of ethyl 2-aminothiazol-4-ylglyoxylate, 4.6 g of p-fluorophenyl isothiocyanate and 20 ml of dimethyl sulphoxide. The resulting product was a pale yellow powder having the following physical properties.

Melting point: 170 to 172 °C

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.32 (3H, triplet, J = 7 Hz),
4.37 (2H, quartet, J = 7 Hz),
7.23 (2H, triplet, J = 9 Hz),

7.5-7.8 (2H, multiplet),
8.37 (1H, singlet),
10.34 (1H, broad singlet),
11.9-12.4 (1H, broad).

PREPARATION 42

Ethyl 2-anilinothiazole-4-carboxylate

A mixture comprising 8.6 g of phenylthiourea, 10 g of ethyl bromopyruvate and 100 ml of ethanol was heated under reflux for 3 hours, and the reaction mixture was then concentrated by evaporation under reduced pressure. A saturated aqueous sodium hydrogen carbonate solution was added to the residue, followed by extraction with ethyl acetate. The extract was dried over anhydrous sodium sulphate and evaporated under reduced pressure. The crystals which formed were collected by filtration, washed with benzene, and then recrystallized from ethanol, to give the desired compound as pale yellow prismatic crystals.

Melting point: 140.5 to 142 °C

Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm:
1.33 (3H, triplet, J = 7 Hz),
4.29 (2H, quartet, J = 7 Hz),
6.98 (1H, triplet, J = 8 Hz),
7.32 (2H, triplet, J = 8 Hz),
7.60 (1H, singlet),
7.72 (2H, doublet, J = 8 Hz),
9.33 (1H, broad singlet).

PREPARATION 43

2-Anilinothiazol-4-ylmethanol

Following a procedure similar to that described in Preparation 15, the desired compound was prepared from 8.5 g of ethyl 2-anilinothiazol-4-carboxylate, 2 g of lithium aluminium hydride and 150 ml of tetrahydrofuran, as colourless flakes having the following physical properties.

Melting point: 115 to 118 °C

Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm:
3.8-4. 4 (1H, broad),
4.58 (2H, singlet),
6.59 (1H, singlet),
6.94 (1H, triplet, J = 8 Hz),
7.30 (2H, triplet, J = 8 Hz),
7.68 (2H, doublet, J = 8 Hz),
8.8-9.4 (1H, broad).

PREPARATION 44

2-Anilinothiazole-4-carbaldehyde

A dimethyl sulphoxide solution (120 ml) of 20 g of sulphur trioxide pyridine complex was added dropwise to a mixture comprising 8.3 g of 2-anilinothiazol-4-ylmethanol, 16.5 ml of triethylamine and 120 ml of dimethyl sulphoxide. The resulting mixture was stirred at room temperature for 10 minutes and then poured into water, followed by extraction with ethyl acetate. The extract was washed successively with aqueous acetic acid, aqueous sodium chloride solution and aqueous sodium hydrogen carbonate solution, and dried over anhydrous sodium sulphate. The residue afforded by evaporation of the solvent under reduced pressure was recrystallized from a mixture of benzene and acetone. The resulting product was a brown powder having the following physical properties.

Melting point: 145 to 147 °C

Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm:

7.03 (1H, triplet, J = 8 Hz),
7.36 (2H, triplet, J = 8 Hz),
7.77 (2H, doublet, J = 8 Hz),
7.83 (1H, singlet),
9.2-9.6 (1H, broad),
9.80 (1H, singlet).

PREPARATION 45

Ethyl 2-o-toluidinothiazole-4-carboxylate

Following a procedure similar to that described in Preparation 42, the desired compound was prepared from 20 g of o-tolylthiourea, 23 g of ethyl bromopyruvate and 200 ml of ethanol, to give the desired compound as pale yellow prismatic crystals having the following physical properties.
Melting point: 130 to 132.5 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm:
1.30 (3H, triplet, J = 7 Hz),
2.34 (3H, singlet),
4.24 (2H, quartet, J = 7 Hz),
7.0-7.4 (3H, multiplet),
7.58 (1H, singlet),
7.89 (1H, doublet, J = 8 Hz),
8.77 (1H, broad singlet).

PREPARATION 46

2-o-Toluidinothiazol-4-ylmethanol

Following a procedure similar to that described in Preparation 15, the desired compound was prepared from 10 g of ethyl 2-o-toluidinothiazole-4-carboxylate, 2.9 g of lithium aluminium hydride and 200 ml of tetrahydrofuran. The resulting product was a brown oil having the following physical properties.
Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm:
2.34 (3H, singlet),
4.56 (2H, singlet),
6.57 (1H, singlet),
6.9-7.4 (3H, multiplet),
7.92 (1H, doublet, J = 8 Hz).

PREPARATION 47

2-o-Toluidinothiazole-4-carbaldehyde

Following a procedure similar to that described in Preparation 44, the desired compound was prepared from 6.12 g of 2-(o-toluidino)thiazole-4-ylmethanol, 13.2 g of a sulphur trioxide pyridine complex, 12 ml of triethylamine and 210 ml of dimethyl sulphoxide, as pale brown prismatic crystals having the following physical properties.
Melting point: 104 to 111 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm:
2.36 (3H, singlet),
6.95-7.4 (3H, multiplet),
7.76 (1H, singlet),
7.97 (1H, doublet, J = 8 Hz),
8.5-8.9 (1H, broad),
9.78 (1H, singlet).

PREPARATION 48

Ethyl 3-(2-anilinothiazol-4-yl)acrylate (Approximately 3 : 1 mixture of E and Z isomers)

A mixture comprising 3.5 g of 2-anilinothiazole-4-carbaldehyde, 6.5 g of (ethoxycarbonylmethylene)triphenylphosphorane and 35 ml of tetrahydrofuran was heated at 60 °C for 2 hours. At the end of this time, the reaction mixture was poured into water and extracted with benzene. The benzene extract was dried over anhydrous sodium sulphate, and the solvent was evaporated off under reduced pressure, to give an oil. This oil was purified by silica gel column chromatography, using as eluent a 9:1 by volume mixture of benzene and ethyl acetate, to give the desired compound as yellow crystals.
Melting point: 113 to 118 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
For the E isomer:
1.27 (3H, triplet, J = 7 Hz),
4.19 (2H, quartet, J = 7 Hz),
6.46 (1H, doublet, J = 16 Hz),
6.97 (1H, triplet, J = 7 Hz),
7.35 (2H, triplet, J = 7 Hz),
7.46 (1H, singlet),
7.46 (1H, doublet, J = 16 Hz),
7.69 (2H, doublet, J = 7 Hz),
10.33 (1H, broad singlet).
For the Z isomer:
1.18 (3H, triplet, J = 7 Hz),
4.17 (2H, quartet, J = 7 Hz),
5.97 (1H, doublet, J = 13 Hz),
6.70 (1H, doublet , J = 13 Hz),
6.9-6.96 (1H, not defined),
7.28 (2H, triplet, J = 7 Hz),
7.44 (1H, singlet),
7.61 (2H, doublet, J = 7 Hz),
10.17 (1H, broad singlet).

PREPARATION 49

(E)-3-(2-Anilinothiazol-4-yl)acrylaldehyde

58 ml of a 1M hexane solution of diisobutyl aluminium hydride was added dropwise at -60 °C to a solution of 4 g of ethyl 3-(2-anilinothiazol-4-yl)acrylate (prepared by the procedure described in Preparation 48) in 40 ml of tetrahydrofuran. The resulting mixture was stirred at -50° C for 2 hours, and then the excess of the reducing reagent was decomposed with 90% aqueous methanol. The mixture was then neutralized with 3N hydrochloric acid and extracted with ethyl acetate. After the extract had been dried over anhydrous sodium sulphate, the solvent was evaporated off under reduced pressure, to give crude 3-(2-anilinothiazol-4-yl)allyl alcohol.

2.6 g of the crude alcohol thus obtained were dissolved in 20 ml of dimethyl sulphoxide, and 3.4 g of triethylamine were added to the resulting solution. Next, a solution of 5.3 g of a sulphur trioxide pyridine complex in dimethyl sulphoxide (10 ml) was added dropwise to the reaction mixture at room temperature, and the mixture was stirred at the same temperature for 30 minutes. The reaction mixture was then poured into water, acidified with 3N hydrochloric acid, and extracted with ethyl acetate. After the extract had been dried over anhydrous sodium sulphate, the solvent was evaporated off under reduced pressure. The residue was purified by silica gel column chromatography, using as eluent a 10:1 by volume mixture of benzene and ethyl acetate, to give the desired compound as pale yellow crystals.
Melting point: 142 to 143 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
6. 67 (1H, doublet of doublets, J = 15 and 8 Hz),
6.98 (1H, triplet, J = 8 Hz),
7.35 (2H, triplet, J = 8 Hz),
7.53 (1H, singlet),
7.54 (1H, doublet, J = 15 Hz),
7.69 (2H, doublet, J = 8 Hz),

9.67 (1H, doublet, J = 8 Hz),
10.38 (1H, broad singlet, disappeared on adding deuterium oxide).

PREPARATION 50

2-(3-p-Bromophenylureido)thiazole-4-carbaldehyde

2.4 g of sodium borohydride were added to a suspension of 5 g of ethyl 2-(3-p-bromophenylureido)thiazol-4-ylglyoxylate in 60 ml of tetrahydrofuran, and then 20 ml of methanol were added dropwise over a period of 1 hour while heating the reaction mixture under reflux; the reaction mixture was thereafter heated under reflux for a further 1 hour. At the end of this time, the reaction mixture was poured into water and neutralized with 3N hydrochloric acid. The crystals which precipitated out were collected by filtration, washed with water and dried, to give crude 1-[2-(3-p-bromophenylureido)thiazol-4-yl]ethane-1,2-diol.
Melting point: 182 to 187 °C (with decomposition)

Subsequently, 4.3 g of the crude diol thus obtained were suspended in 200 ml of tetrahydrofuran, and an aqueous solution (30 ml) of 5.1 g of sodium metaperiodate was added dropwise to it under ice-cooling. The resulting mixture was stirred at the same temperature for 1 hour, and then for a further 1 hour at room temperature. The reaction mixture was then poured into ice water and the crystals which precipitated out were collected by filtration. The resulting product was a white powder having the following physical properties.
Decomposition point: circa 250 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
7.47 and 7.50 (4H, A_2B_2, J = 9 Hz),
8.24 (1H, singlet),
9.16 (1H, broad singlet),
9.75 (1H, singlet),
10.93 (1H, broad singlet).

PREPARATION 51

(E)-3-[2-(3-p-Bromophenylureido)thiazol-4-yl]allyl alcohol

Following a procedure similar to that described in Preparation 48, crude ethyl 3-[2-(3-p-bromophenylureido)thiazol-4-yl]acrylate was prepared from 1 g of 2-(3-p-bromophenylureido)thiazole-4-carbaldehyde, 1.2 g of ethoxycarbonylmethylenetriphenylphosphorane and 20 ml of tetrahydrofuran. Subsequently, following a procedure similar to that described in Preparation 49, the desired compound was prepared from 1.1 g of the above crude ethyl ester, 14 ml of a 1M hexane solution of diisobutyl aluminium hydride and 30 ml of tetrahydrofuran. The resulting product was a white powder having the following physical properties.
Decomposition point: circa 220 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
4.10 (2H, doublet of doublets, J = 5 and 3 Hz, converted to doublet (J = 3 Hz) on adding deuterium oxide),
4.84 (1H, triplet, J = 5 Hz, disappeared on adding deuterium oxide),
6.40 (1H, doublet of doublets, J = 16 and 3 Hz),
6.47 (1H, doublet, J = 16 Hz),
6.94 (1H, singlet),
7.46 and 7.48 (4H, A_2B_2, J = 9 Hz),
9.15 (1H, broad singlet, disappeared on adding deuterium oxide),
10.66 (1H, broad singlet, disappeared on adding deuterium oxide).

PREPARATION 52

(E)-3-[2-(3-p-Bromophenylureido)thiazol-4-yl]acrylaldehyde

Following a procedure similar to that described in Preparation 49, the desired compound was prepared from 0.84 g of (E-3-[2-(3-p-bromophenylureido)thiazol-4-yl]allyl alcohol, 1.13 g of a sulphur trioxide pyridine complex, 0.72 g of triethylamine and 20 ml of dimethyl sulphoxide. The resulting product was a pale brown powder having the following physical properties.

Decomposition point: circa 260 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
6.61 (1H, doublet of doublets, J = 15 and 8 Hz),
7.4-7.55 (4H, multiplet),
7.61 (1H, doublet, J = 15 Hz),
7.73 (1H, singlet),
9.13 (1H, singlet, disappeared on adding deuterium oxide),
9.66 (1H, doublet, J = 8 Hz),
10.6-11.2 (1H, broad, disappeared on adding deuterium oxide).

PREPARATION 53

Ethyl 2-[bis(p-fluorophenyl)methylamine]thiazol-4-ylglyoxylate

A mixture comprising 1.01 g of ethyl 2-aminothiazol-4-ylglyoxylate, 1.48 g of bis(p-fluorophenyl)methyl chloride, 0.75 g of triethylamine, 3 ml of dimethylformamide and 0.35 g of pulverized potassium iodide was srirred at 85 to 90 °C for 7.5 hours. After the reaction mixture had been cooled, a saturated aqueous sodium hydrogen carbonate solution was added thereto, followed by extraction with ethyl acetate. The extract was dried over anhydrous sodium sulphate and the solvent was evaporated off under reduced pressure. The residue was purified by silica gel column chromatography, using as eluent a 10:1 by volume mixture of benzene and ethyl acetate. The resulting product was recrystallized from benzene, to give the desired compound as yellow crystals having the following physical properties.
Melting point: 122 to 124 °C
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.25 (3H, triplet, J = 7 Hz),
4.29 (2H, quartet, J = 7 Hz),
6.05 (1H, doublet, J = 8 Hz),
7.12-7.21 (4H, multiplet),
7.33-7.42 (4H, multiplet),
8.01 (1H, singlet),
8.92 (1H, doublet, J = 8 Hz),

PREPARATION 54

Ethyl 2-diphenylmethylaminothiazol-4-ylglyoxylate

Following a procedure similar to that described in Preparation 53, the desired compound was prepared from 10.1 g of 2-aminothiazol-4-ylglyoxylate, 10.0 g of diphenylmethyl chloride, 10 ml of triethylamine, 10 ml of dimethylformamide and 1.0 g of potassium iodide. The resulting product was a yellow powder having the following physical properties.
Melting point: 82 to 85 °C
Nuclear Magnetic Resonance Spectrum ($CDC\ell_3$) δ ppm:
1.38 (3H, triplet, J = 7 Hz),
4. 38 (2H, quartet, J = 7 Hz),
5.64 (1H, doublet, J = 6 Hz),
6.04 (1H, broad doublet, J = 6 Hz),
7.3-7.4 (10H, multiplet),
7.86 (1H, singlet).

PREPARATION 55

1-(2-Diphenylaminothiazol-4-yl)ethane-1,2-diol

Following a procedure similar to that described in Preparation 50, the desired compound was prepared from 1.68 g of ethyl 2-diphenylmethylaminothiazol-4-ylglyoxylate, 0.35 g of sodium borohydride, 3 ml of methanol and 8 ml of tetrahydrofuran. The resulting product was a white powder having the following physical properties.

Softening point: 143 to 148 °C
Nuclear Magnetic Resonance Spectrum ($CDC\ell_3$) δ ppm:
3.73 (1H, doublet of doublets, J = 11 and 4 Hz),
3.81 (1H, doublet of doublets, J = 11 and 4 Hz),
3.8-4.3 (2H, broad, disappeared on adding deuterium oxide),
4.58 (1H, triplet, J = 4 Hz),
5.57 (1H, singlet),
6.33 (1H, singlet),
7.2-7.35 (10H, multiplet).

PREPARATION 56

2-Diphenylmethylaminothiazole-4-carbaldehyde

Following a procedure similar to that described in Preparation 50, the desired compound was prepared from 2.11 g of 1-(2-diphenylmethylaminothiazol-4-yl)ethane-1,2-diol, 3.15 g of sodium metaperiodate, 40 ml of water and 20 ml of methanol. The resulting product was a pale brown foam having the following physical properties.
Nuclear Magnetic Resonance Spectrum ($CDC\ell_3$) δ ppm:
5.68 (1H, singlet),
7.3-7.4 (11H, not defined),
9.65 (1H, singlet).
Mass spectrum (m/e): 294 (M^+).

PREPARATION 57

Ethyl 2-p-fluoroanilinothiazole-4-carboxylate

The reaction described in Preparation 42 was repeated, but using 12 g of p-fluorophenylthiourea, 14.8 g of ethyl bromopyruvate, and 120 ml of ethanol, to give the title compound as pale yellow prisms.
Melting point: 133 to 136 °C.
Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm:
1.34 (3H, triplet, J=7 Hz),
4.31 (2H, quartet, J=7 Hz),
7.10 (2H, triplet, J=9 Hz),
7.65 (1H, singlet),
7.78 (2H, doublet of doublets, J=9 and 5 Hz),
9.2.-9.6 (1H, broad).

PREPARATION 58

2-p-Fluoroanilinothiazol-4-ylmethanol

The reaction described in Preparation 50 was repeated, but using 12.04 g of ethyl 2-p-fluoroanilinothiazole-4-carboxylate, 6 g of sodium borohydride, 120 ml of anhydrous tetrahydrofuran, and 70 ml of absolute methanol, to give the title compound as colourless prisms.
Melting point: 156 to 161 °C.
Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm:
4.05 (1H, broad triplet, J=5 Hz),
4.56 (2H, broad doublet, J=5 Hz),
6.60 (1H, singlet),
7.07 (2H, triplet, J=9 Hz),
7.74 (2H, doublet of doublets, J=9 and 5 Hz),
8.9-9.4 (1H, broad).

PREPARATION 59

2-p-Fluoroanilinothiazole-4-carbaldehyde

The reaction described in Preparation 44 was repeated, but using 3.03 g of 2-p-fluoroanilinothiazol-4-ylmethanol, 8.5 g of pyridine sulphur trioxide complex, 7.5 ml of triethylamine and 140 ml of dimethyl sulphoxide, to give the title compound as pale brown prisms.
Melting point: 152 to 155 °C.
Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm:
7.12 (2H, triplet, J=9 Hz),
7.7-7.9 (2H, not defined),
7.86 (1H, singlet),
9.3-9.7 (1H, broad),
9.83 (1H, singlet).

PREPARATION 60

Ethyl 2-p-anisidinothiazole-4-carboxylate

The reaction described in Preparation 42 was repeated, but using 10.03 g of 4-methoxyphenylthiourea, 10 g of ethyl bromopyruvate, and 100 ml of ethanol, to give the title compound as pale yellow prisms.
Melting point: 119 to 120.5 °C.
Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm:
1.33 (3H, triplet, J=7 Hz),
3.80 3H, singlet,),
4.29 (2H, quartet, J=7 Hz),
6.94 (2H, doublet, J=9 Hz),
7.55-7.7 (3H, not defined),
9.13 (1H, broad singlet).

PREPARATION 61

2-p-Anisidinothiazol-4-ylmethanol

The reaction described in Preparation 15 was repeated, but using 5.0 g of ethyl 2-p-anisidinothiazole-4-carboxylate, 1.5 g of lithium aluminium hydride and 100 ml of anhydrous tetrahydrofuran, to give the title compound as a pale red powder.
Melting point: 104 to 105 °C.
Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm:
3.80 (3H, singlet),
3.8-4.3 (1H, broad),
4.56 (2H, broad singlet),
6.53 (1H, singlet),
6.91 (2H, doublet, J=9 Hz),
7.59 (2H, doublet, J=9 Hz),
8.7-9.1 (1H, broad).

PREPARATION 62

2-p-Anisidinothiazole-4-carbaldehyde

The reaction described in Preparation 44 was repeated, but using 3 g of 2-p-anisidinothiazol-4-ylmethanol, 6.1 g of pyridine sulphur trioxide complex, 5.3 ml of triethylamine and 90 ml of dimethyl sulphoxide, to give the

title compound as pale brown crystals.
Melting point: 108 to 110°C.
Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm:
3.80 (3H, singlet),
6.94 (2H, doublet, J=9 Hz),
7.65 (2H, doublet, J=9 Hz),
7.76 (1H, singlet),
9.0-9.4 (1H, broad),
9.79 (1H, singlet).

PREPARATION 63

Ethyl 2-m-trifluoromethylanilinothiazole-4-carboxylate

The reaction described in Preparation 42 was repeated, but using 10.02 g of m-trifluoromethylphenylthiourea, 8.8 g of ethyl bromopyruvate and 100 ml of ethanol, to give the title compound as pale yellow crystals.
Melting point: 124.5 to 127 °C.
Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm:
1.36 (3H, triplet, J=7 Hz),
4.31 (2H, quartet, J=7 Hz),
7.25-7.7 (2H, not defined),
7.75 (1H, singlet),
7.97 (1H, broad doublet, J=8 Hz),
8.35 (1H, broad singlet),
9.6-9.9 (1H, broad).

PREPARATION 64

2-m-Trifluoromethylanilinothiazol-4-ylmethanol

The reaction described in Preparation 15 was repeated, but using 3.92 g of ethyl 2-m-trifluoromethylanilinothiazole-4-carboxylate, 1 g of lithium aluminium hydride and 80 ml of anhydrous tetrahydrofuran, to give the title compound as a colourless powder.
Melting point: 126.5 to 128 °C.
Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm:
4.16 (1H, broad triplet, J=5 Hz),
4.61 (2H, broad doublet , J=5 Hz),
6.70 (1H, singlet),
7.26 (1H, broad doublet, J=8 Hz),
7.53 (1H, triplet, J=8 Hz),
7.99 (1H, broad doublet, J=8 Hz),
8.17 (1H, broad singlet),
9.1-9.9 (1H, broad).

PREPARATION 65

2-m-Trifluoromethylanilinothiazole-4-carbaldehyde

The reaction described in Preparation 44 was repeated, but using 2.65 g of 2-m-trifluoromethylanilinothiazol-4-ylmethanol, 4.8 g of pyridine sulphur trioxide complex, 4.2 ml of triethylamine and 90 ml of dimethyl sulphoxide, to give the title compound as a pale brown powder.
Melting point: 151 to 153 °C.
Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm:
7.34 (1H, broad doublet, J=8 Hz),
7.58 (1H, triplet, J=8 Hz),
7.94 (1H, singlet),

8.06 (1H, broad doublet, J=8 Hz),
8.26 (1H, broad singlet),
9.6-10.0 (1H, broad),
9.87 (1H, singlet).

PREPARATION 66

Ethyl 2-ethylaminothiazole-4-carboxylate

The reaction described in Preparation 42 was repeated, but using 10 g of ethylthiourea, 20 g of ethyl bromopyruvate and 100 ml of ethanol, to give the title compound as a pale yellow powder.
Melting point: 93 to 95 °C.
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.17 (3H, triplet, J=7 Hz),
1.28 (3H, triplet, J=7 Hz),
3.1-3.4 (2H, not defined), 4.23 (2H, quartet, J=7 Hz),
7.51 (1H, singlet),
7.76 (1H, broad triplet, J=5 Hz).

PREPARATION 67

2-Ethylaminothiazol-4-ylmethanol

The reaction described in Preparation 17 was repeated, but using 10 g of ethyl 2-ethylaminothiazole-4-carboxylate, 3.8 g of sodium borohydride, 70 ml of methanol and 150 ml of tetrahydrofuran, to give the title compound as a yellow oil.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.30 (3H, triplet, J=7 Hz),
3.24 (2H, quartet, J=7 Hz),
4.51 (2H, singlet),
6.2-6.5 (3H, not defined, changed to 6.34 (1H, singlet) on adding deuterium oxide).

PREPARATION 68

2-Ethylaminothiazole-4-carbaldehyde

The reaction described in Preparation 44 was repeated, but using 4.4 g of 2-ethylaminothiazol-4-ylmethanol, 13.3 g of sulphur trioxide pyridine complex, 8.4 g of triethylamine and 60 ml of dimethyl sulphoxide, to give the title compound as pale brown prisms.
Melting point: 84 to 85 °C.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.32 (3H, triplet, J=7 Hz),
3.2-3.6 (2H, multiplet),
6.3-6.7 (1H, broad),
7.40 (1H, singlet),
9.70 (1H, singlet).

PREPARATION 69

Ethyl 2-allylaminothiazole-4-carboxylate

The reaction described in Preparation 42 was repeated, but using 20 g of allylthiourea, 37 g of ethyl bromopyruvate and 200 ml of ethanol, to give the title compound as a pale yellow powder.

Melting point: 85 to 86 °C.
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.26 (3H, triplet, J=7 Hz),
3.84-3.90 (2H, multiplet),
4.21 (2H, quartet, J=7 Hz),
5.13 (1H, doublet of doublets of doublets, J=10, 3 and 1.5 Hz),
5.24 (1H, doublet of doublets of doublets, J=17, 3 and 1.5 Hz),
5.8-5.97 (1H, multiplet),
7.51 (1H, singlet),
7.96 (1H, broad triplet, J=5 Hz).

PREPARATION 70

2-allylaminothiazol-4-ylmethanol

The reaction described in Preparation 15 was repeated, but using 10 g of ethyl 2-allylaminothiazole-4-carboxylate, 2.7 g of lithium aluminium hydride and 150 ml of tetrahydrofuran, to give the title compound as pale brown needles.
Melting point: 74 to 75 °C.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
3.1-3.9 (1H, broad),
3.86 (2H, broad doublet, J=5 Hz),
4.51 (2H, singlet),
5.1-5.45 (2H, multiplet),
5.5-6.2 (2H, multiplet),
6.37 (1H, singlet).

PREPARATION 71

2-Allylaminothiazole-4-carbaldehyde

The reaction described in Preparation 44 was repeated, but using 11 g of 2-allylaminothiazol-4-ylmethanol, 31 g of sulphur trioxide pyridine complex, 20 g of triethylamine and 100 ml of dimethyl sulphoxide, to give the title compound as pale brown needles.
Melting point: 106 to 107°C.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
4.05 (2H, broad singlet),
5.1-5.5 (2H, multiplet),
5.7-6.15 (1H, multiplet),
7.3-7.7 (1H, broad),
7.40 (1H, singlet),
9.69 (1H, singlet).

PREPARATION 72

Ethyl 2-cyclohexylaminothiazole-4-carboxylate

The reaction described in Preparation 42 was repeated, but using 17 g of cyclohexylthiourea, 22 g of ethyl bromopyruvate and 200 ml of ethanol, to give the title compound as a yellow oil.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.0-2.3 (10H, multiplet),
1.37 (3H, triplet, J=7 Hz),
3.0-3.5 (1H, multiplet),
4.34 (2H, quartet, J=7 Hz),
5.1-5.6 (1H, multiplet),
7.41 (1H, singlet).

PREPARATION 73

2-Cyclohexylaminothiazol-4-ylmethanol

The reaction described in Preparation 15 was repeated, but using 19 g of ethyl 2-cyclohexylaminothiazole-4-carboxylate, 4.2 g of lithium aluminium hydride and 250 ml of tetrahydrofuran, to give the title compound as pale yellow needles.
Melting point: 118 to 120 °C.
Nuclear Magnetic Resonance Spectrum ($CDC\ell_3$) δ ppm:
1.0-2.2 (10H, multiplet),
2.9-3.5 (2H, not defined),
4.50 (2H, singlet),
5.0-5.5 (1H, broad),
6.33 (1H, singlet).

PREPARATION 74

2-Cyclohexylaminothiazole-4-carbaldehyde

The reaction described in Preparation 44 was repeated, but using 10 g of 2-cyclohexylaminothiazol-4-ylmethanol, 22.4 g of sulphur trioxide pyridine complex, 14.3 g of triethylamine and 100 ml of dimethyl sulphoxide, to give the title compound as a pale brown oil.
Nuclear Magnetic Resonance Spectrum ($CDC\ell_3$) δ ppm:
1.0-2.2 (10H, multiplet),
3.2-3.6 (1H, multiplet),
5.1-5.4 (1H, multiplet),
7.40 (1H, singlet),
9.72 (1H, singlet).

PREPARATION 75

Ethyl 2-diphenylaminothiazole-4-carboxylate

The reaction described in Preparation 42 was repeated, but using 20 g of 1,1-diphenylthiourea, 19 g of ethyl bromopyruvate and 200 ml of ethanol, to give the title compound as an orange oil.
Nuclear Magnetic Resonance Spectrum ($CDC\ell_3$) δ ppm:
1.36 (3H, triplet, J=7 Hz),
4.35 (2H, quartet, J=7 Hz),
7.1-7.5 (10H, multiplet),
7 .54 (1H, singlet).

PREPARATION 76

2-Diphenylaminothiazol-4-ylmethanol

The reaction described in Preparation 15 was repeated, but using 27 g of ethyl 2-diphenylaminothiazole-4-carboxylate, 4.7 g of lithium aluminium hydride and 400 ml of tetrahydrofuran, to give the title compound as pale yellow prisms.
Melting point: 136 to 138 °C.
Nuclear Magnetic Resonance Spectrum ($CDC\ell_3$) δ ppm:
2.33 (1H, broad triplet, J=6 Hz),
4.56 (2H, broad doublet, J=6 Hz),

6.52 (1H, singlet),
7.1-7.5 (10H, multiplet).

PREPARATION 77

2-Diphenylaminothiazole-4-carbaldehyde

The reaction described in Preparation 44 was repeated, but using 10 g of 2-diphenylaminothiazol-4-ylmethanol, 16.8 g of sulphur trioxide pyridine complex, 10.7 g of triethylamine and 100 ml of dimethyl sulphoxide, to give the title compound as pale yellow prisms.
Melting point: 160 to 161 °C.
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
7.2-7.6 (10H, multiplet),
8.06 (1H, singlet),
9.70 (1H, singlet).

PREPARATION 78

Ethyl 2-morpholinothiazole-4-carboxylate

The reaction described in Preparation 26 was repeated, but using 1.4 g of morpholine, 3 g of ethyl 2-chlorothiazole-4-carboxylate, 3 g of triethylamine and 12 ml of dimethylformamide, to give the title compound as colourless needles.
Melting point: 84 to 86 °C.
Nuclear Magnetic Resonance Spectrum ($CDC\ell_3$) δ ppm:
1.37 (3H, triplet, J=7 Hz),
3.45-3.6 (4H, multiplet),
3.75-3.9 (4H, multiplet),
4.36 (2H, quartet, J=7 Hz),
7.50 (1H, singlet).

PREPARATION 79

2-Morpholinothiazol-4-ylmethanol

The reaction described in Preparation 15 was repeated, but using 3.7 g of ethyl 2-morpholinothiazole-4-carboxylate, 0.6 g of lithium aluminium hydride and 50 ml of tetrahydrofuran, to give the title compound as white needles.
Melting point: 120 to 121 °C.
Nuclear Magnetic Resonance Spectrum ($CDC\ell_3$) δ ppm:
2.40 (1H, triplet, J=6 Hz),
3.35-3.55 (4H, multiplet),
3.7-3.9 (4H, multiplet),
4.59 (2H, doublet, J=6 Hz),
6.47 (1H, singlet).

PREPARATION 80

2-Morpholinothiazole-4-carbaldehyde

The reaction described in Preparation 44 was repeated, but using 2.4 g of 2-morpholinothiazol-4-ylmethanol, 5.7 g of sulphur trioxide pyridine complex, 3.6 g of triethylamine and 30 ml of dimethyl sulphoxide, to give the

title compound as pale yellow needles.
Melting point: 107 to 108 °C.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
3.45-3.65 (4H, multiplet),
3.75-3.9 (4H, multiplet),
7.51 (1H, singlet),
9.77 (1H, singlet).

PREPARATION 81

Ethyl 2-piperidinothiazole-4-carboxylate

A mixture comprising 2.1 g of piperidine, 4 g of ethyl 2-chlorothiazole-4-carboxylate, 4.2 g of triethylamine and 20 ml of benzene was heated under reflux for 12 hours. At the end of this time, the reaction mixture was poured into water and extracted with benzene. The extract was washed with water, dried over anhydrous magnesium sulphate and concentrated by evaporation under reduced pressure. The residue was then purified by silica gel column chromatography, using as eluent a 10:1 by volume mixture of benzene and ethyl acetate, to give the title compound as a pale yellow oil.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.36 (3H, triplet, J=7 Hz),
1.5-1.9 (6H, multiplet),
3.3-3.7 (4H, multiplet),
4.35 (2H, quartet, J=7 Hz),
7.42 (1H, singlet).

PREPARATION 82

2-Piperidinothiazol-4-ylmethanol

The reaction described in Preparation 15 was repeated, but using 3.0 g of ethyl 2-piperidinothiazole-4-carboxylate, 0.5 g of lithium aluminium hydride and 50 ml of tetrahydrofuran, to give the title compound as pale yellow prisms.
Melting point: 89 to 90 °C.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.5-1.9 (6H, multiplet),
2.50 (1H, broad),
3.3-3.6 (4H, multiplet),
4.45-4.65 (2H, broad doublet),
6.37 (1H, singlet).

PREPARATION 83

2-Piperidinothiazole-4-carbaldehyde

The reaction described in Preparation 44 was repeated, but using 2.4 g of 2-piperidinothiazol-4-ylmethanol, 5.8 g of sulphur trioxide pyridine complex, 3.7 g of triethylamine and 30 ml of dimethyl sulphoxide, to give the title compound as pale orange prisms.
Melting point: 68 to 69 °C.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.55-1.85 (6H, multiplet),
3.4-3.7 (4H, multiplet),
7.44 (1H, singlet),
9.75 (1H, singlet).

PREPARATION 84

Ethyl 2-(Thiomorpholin-4-yl)thiazole-4-carboxylate

The reaction described in Preparation 26 was repeated, but using 1.53 g of thiomorpholine, 2.36 g of ethyl 2-bromothiazole-4-carboxylate, 2.02 g of triethylamine and 40 ml of dimethylformamide, to give the title compound as a pale yellow powder.

Melting point: 99 to 100 °C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.37 (3H, triplet, J=7 Hz),
2.7-2.75 (4H, multiplet),
3.85-3.9 (4H, multiplet),
4.35 (2H, quartet, J=7 Hz),
7.44 (1H, singlet).

PREPARATION 85

2-(Thiomorpholin-4-yl)thiazol-4-ylmethanol

The reaction described in Preparation 15 was repeated, but using 1.5 g of ethyl 2-(thiomorpholin-4-yl)thiazole-4-carboxylate, 0.26 g of lithium aluminium hydride and 15 ml of tetrahydrofuran, to give the title compound as a colourless powder.

Melting point: 83 to 84 °C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
2.51 (1H, broad doublet, J=5 Hz, disappeared on adding deuterium oxide),
2.68-2.73 (4H, multiplet),
3.8-3.85 (4H, multiplet),
4.53 (2H, doublet, J=5 Hz, changed to 4.51 (2H, singlet) on adding deuterium oxide),
6.41 (1H, triplet, J=1 Hz).

PREPARATION 86

2-(Thiomorpholin-4-yl)thiazole-4-carbaldehyde

The reaction described in Preparation 44 was repeated, but using 1.2 g of 2-(thiomorpholin-4-yl)thiazol-4-ylmethanol, 2.65 g of sulphur trioxide pyridine complex, 1.68 g of triethylamine and 30 ml of dimethyl sulphoxide, to give the title compound as a colourless powder.

Melting Point: 69 to 71 °C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
2.7-2.76 (4H, multiplet),
3.85-3.93 (4H, multiplet),
7.47 (1H, singlet),
9.69 (1H, singlet).

PREPARATION 87

Ethyl 2-(4-Methyl-1-piperazinyl)thiazole-4-carboxylate

The reaction described in Preparation 26 was repeated, but using 2.5 g of N-methylpiperazine, 4.0 g of ethyl 2-chlorothiazole-4-carboxylate, 4.2 g of triethylamine and 30 ml of toluene, to give the title compound as a pale yellow oil.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.37 (3H, triplet, J=7 Hz),

2.34 (3H, singlet),
2.51 (4H, broad triplet, J=6 Hz),
3.56 (4H, broad triplet, J=6 Hz),
4.35 (2H, quartet, J=7 Hz),
7.46 (1H, singlet).

PREPARATION 88

2-(4-Methyl-1-piperazinyl)thiazol-4-ylmethanol

The reaction described in Preparation 15 was repeated, but using 4.0 g of ethyl 2-(4-methyl-1-piperazinyl)thiazole-4-carboxylate, 0.6 g of lithium aluminium hydride and 50 ml of tetrahydrofuran, to give the title compound as white prisms.
Melting Point: 103 to 105 °C.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
2.26 (3H, singlet),
2.43 (4H, broad triplet, J=5 Hz),
2.6-2.8 (1H, broad),
3.41 (4H, broad triplet, J=5 Hz),
4.47 (2H, singlet),
6.34 (1H, triplet, J=1 Hz),

PREPARATION 89

2-(4-Methyl-1-piperazinyl)thiazole-4-carbaldehyde

The reaction described in Preparation 44 was repeated, but using 2.4 g of 2-(4-methyl-1-piperazinyl)thiazol-4-ylmethanol, 5.4 g of sulphur trioxide pyridine complex, 3.4 g of triethylamine, and 30 ml of dimethyl sulphoxide, to give the title compound as a pale brown oil.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
2.35 (3H, singlet),
2.53 (4H, broad triplet, J=5 Hz),
3.59 (4H, broad triplet, J=5 Hz),
7.47 (1H, singlet),
9.70 (1H, singlet).

PREPARATION 90

Ethyl 2-octylaminothiazole-4-carboxylate

The reaction described in Preparation 26 was repeated, but using 2.7 g of octylamine, 4.0 g of ethyl 2-chlorothiazole-4-carboxylate, 4.2 g of triethylamine and 15 ml of dimethylformamide, to give the title compound as a pale yellow oil.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
0.7-1.9 (18H, not defined),
3.0-3.4 (2H, multiplet),
4.36 (2H, quartet, J=7 Hz),
5.5-6.0 (1H, broad),
7.41 (1H, singlet).

PREPARATION 91

2-Octylaminothiazol-4-ylmethanol

The reaction described in Preparation 15 was repeated, but using 1.5 g of 2-octylaminothiazol-4-carboxylate, 0.2 g of lithium aluminium hydride and 30 ml of tetrahydrofuran, to give the title compound as a pale yellow oil.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
0.88 (3H, broad triplet, J=7 Hz),
1.2-1.45 (10H, multiplet),
1.55-1.75 (2H, multiplet),
3.15-3.3 (2H, multiplet),
4.51 (2H, doublet, J=1 Hz),
5.26 (1H, broad singlet),
6.34 (1H, singlet).

PREPARATION 92

2-Octylaminothiazole-4-carbaldehyde

The reaction described in Preparation 44 was repeated, but using 1.3 g of 2-octylaminothiazol-4-ylmethanol, 2.6 g of pyridine sulphur trioxide complex, 1.6 g of triethylamine and 20 ml of dimethyl sulphoxide, to give the title compound as pale brown needles.
Melting point: 60 to 62 °C.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
0.7-1.9 (15H, multiplet),
3.1-3.6 (2H, multiplet),
5.9-6.3 (1H, broad),
7.41 (1H, singlet),
9.72 (1H, singlet).

PREPARATION 93

Ethyl 2-isopropylaminothiazole-4-carboxylate

The reaction described in Preparation 42 was repeated, but using 3.7 g of isopropylthiourea, 7.4 g of ethyl bromopyruvate and 50 ml of ethanol, to give the title compound as a pale yellow oil.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.29 (6H, doublet, J=7 Hz),
1.37 (3H, triplet, J=7 Hz),
3.35-3.85 (1H, multiplet),
4.35 (2H, quartet, J=7 Hz),
5.0-5.7 (1H, broad),
7.42 (1H, singlet).

PREPARATION 94

2-Isopropylaminothiazol-4-ylmethanol

The reaction described in Preparation 15 was repeated, but using 6.8 g of ethyl 2-isopropylaminothiazole-4-carboxylate, 1.2 g of lithium aluminium hydride and 100 ml of tetrahydrofuran, to give the title compound as a pale yellow oil.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
2.27 (6H, doublet, J=7 Hz),
3.4-3.9 (1H, multiplet),
4.51 (2H, singlet),
4.8-5.3 (1H, broad),

6.34 (1H, singlet).

PREPARATION 95

2-Isopropylaminothiazole-4-carbaldehyde

The reaction described in Preparation 44 was repeated, but using 4.4 g of 2-isopropylaminothiazol-4-ylmethanol, 12.2 g of pyridine sulphur trioxide complex, 7.7 g of triethylamine and 60 ml of dimethyl sulphoxide, to give the title compound as a pale brown oil:
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
2.31 (6H, doublet, J=7 Hz),
3.55-4.0 (1H, multiplet),
5.1-5.5 (1H, broad),
7.41 (1H, singlet),
9.74 (1H, singlet).

PREPARATION 96

Ethyl 2-benzylaminothiazole-4-carboxylate

The reaction described in Preparation 42 was repeated, but using 5.02 g of benzylthiourea, 5.87 g of ethyl bromopyruvate and 50 ml of ethanol, to give the title compound as pale yellow needles.
Melting Point: 132 to 136 °C.
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
1.27 (3H, triplet, J=7 Hz),
4.22 (2H, quartet, J=7 Hz),
4.47 (2H, doublet, J=6 Hz),
7.1-7.6 (5H, multiplet),
7.53 (1H, singlet),
8.30 (1H, broad triplet, J=6 Hz),

PREPARATION 97

2-Benzylaminothiazol-4-ylmethanol

The reaction described in Preparation 15 was repeated, but using 5 g of ethyl 2-benzylaminothiazole-4-carboxylate, 1.4 g of lithium aluminium hydride and 100 ml of tetrahydrofuran, to give the title compound as colourless needles.
Melting Point: 85 to 86.5 °C.
Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm:
3.7-4.1 (1H, broad),
4.44 (2H, broad singlet),
4.54 (2H, broad singlet),
6.38 (1H, singlet),
6.9-7.3 (1H, broad),
7.2-7.4 (5H, multiplet),

PREPARATION 98

2-Benzylaminothiazole-4-carbaldehyde

The reaction described in Preparation 44 was repeated, but using 1.21 g of 2-benzylaminothiazol-4-ylmethanol, 2. 6 g of pyridine sulphur trioxide complex, 3 ml of triethylamine and 30 ml of dimethyl sulphoxide, to give

the title compound as pale brown crystals.
Melting Point: 162 to 165 °C.
Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm:
4.44 (2H, broad doublet, J=5 Hz),
7.2-7.5 (5H, multiplet),
7.5-7.9 (1H, broad),
7.65 (1H, singlet),
9.71 (1H, singlet).

PREPARATION 99

Sodium 2-(3-benzoylthioureido)thiazol-4-ylglyoxylate

A mixture comprising 2.0 g of ethyl 2-(3-benzoylthioureido)thiazol-4-ylglyoxylate, 2.3 g of potassium carbonate, 100 ml of acetone, 100 ml of methanol and 20 ml of water was stirred for 50 minutes at 60 °C, after which the solvent was evaporated off under reduced pressure. Ethyl acetate and brine were added to the residue, to give the crude title compound as a yellow powder.
Melting point: 223 to 226 °C.
Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide) δ ppm:
7.35-7.6 (3H, multiplet),
7.70 (1H, singlet),
7.92 (2H, broad doublet, J=7 Hz),
9.4-10.0 (1H, broad, disappeared on adding deuterium oxide).

PREPARATION 100

Ethyl 2-cyclopropylaminothiazole-4-carboxylate

The reaction described in Preparation 26 was repeated, except that a mixture comprising 2.28 g of cyclopropylamine, 5.0 g of ethyl 2-bromothiazole-4-carboxylate and 20 ml of toluene was heated at 100-110 °C for 16 hours in a sealed tube, to give the title compound as a pale yellow oil.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
0.5-0.9 (4H, multiplet),
1.37 (3H, triplet, J=7 Hz),
2.45-2.75 (1H, multiplet),
4.36 (2H, quartet, J=7 Hz),
5.8-6.1 (1H, broad),
7.48 (1H, singlet).

PREPARATION 101

2-Cyclopropylaminothiazol-4-ylmethanol

The reaction described in Preparation 15 was repeated, but using 1.2 g of ethyl 2-cyclopropylaminothiazole-4-carboxylate, 0.2 g of lithium aluminium hydride and ml of tetrahydrofuran, to give the title compound as a pale yellow oil.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
0.6-1.0 (4H, multiplet),
2.45-2.7 (1H, multiplet),
3.1-4.0 (1H, broad),
4.53 (2H, singlet),
5.9-6.7 (1H, broad),
6.42 (1H, singlet).

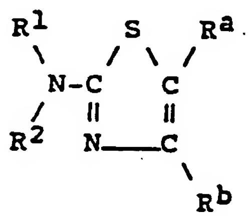
PREPARATION 102

2-Cyclooropylaminothiazole-4-carbaldebyde

The reaction described in Preparation 44 was repeated, but using 1.1 g of 2-cyclopropylaminothiazol-4-ylmethanol, 3.1 g of sulphur trioxide pyridine complex, 2 g of triethylamine and 15 ml of dimethyl sulphoxide, to give the title compound as pale yellow prisms.
Melting point: 124 to 127 °C.
Nuclear Magnetic Resonance Spectrum ($CDC\ell_3$) δ ppm:
0.6-1.0 (4H, multiplet),
1.55-1.8 (1H, multiplet),
6.7-7.3 (1H, broad),
7.48 (1H, singlet),
9.76 (1H, singlet).

Claims

1. Compounds of formula (I):

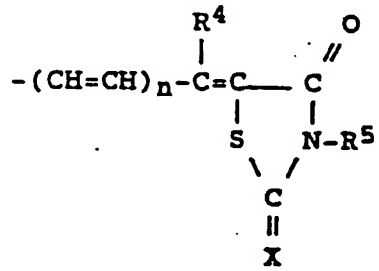


(I)

in which:
R^1 and R^2 are the same or different and each represents:
a hydrogen atom,
a C_1 - C_{12} alkyl group,
a C_3 - C_6 aliphatic hydrocarbon group having one or two carbon-carbon double or treble bonds,
a C_3 - C_8 cycloalkyl group,
a C_6 - C_{14} aryl group,
a substituted C_6 - C_{14} aryl group having at least one of substituents (a) defined below,
an aralkyl or substituted aralkyl group with from 1 to 3 aryl parts each of which is C_6 - C_{14} and an alkyl part which is C_1 - C_6, and said substituted aralkyl groups having at least one of substituents (a) defined below,
a C_1 - C_{12} alkanoyl group,
a C_3 - C_{12} alkenoyl group,
a C_4 - C_9 cycloalkylcarbonyl group,
a C_7 - C_{15} arylcarbonyl group,
a substituted C_7 - C_{15} arylcarbonyl group having at least one of substituents (a) defined below,
an arylalkanoyl group in which the aryl part is C_6 - C_{14} and is unsubstituted or has at least one of substituents (a) defined below and the alkanoyl part is C_2 - C_6,
an arylalkenoyl group in which the aryl part is C_6 - C_{14} and is unsubstituted or has at least one of substituents (a) defined below and the alkenoyl part is C_3 - C_6,
a C_2 - C_7 alkoxycarbonyl group,
a C_7 - C_{15} aryloxycarbonyl group,
a substituted C_7 - C_{15} aryloxycarbonyl group having at least one of substituents (a) defined below,
a C_8 - C_{20} aralkyloxycarbonyl group,
a substituted C_8 - C_{20} aralkyloxycarbonyl group having at least one of substituents (a) defined below,
a group of formula $-CONR^6R^7$,
a group of formula $-CSNR^6R^7$,
a C_1 - C_6 alkylsulphonyl group,
a C_1 - C_6 haloalkylsulphonyl group,
a C_6 - C_{14} arylsulphonyl group,
a substituted C_6 - C_{14} arylsulphonyl group having at least one of substituents (a) defined below,
a C_1 - C_6 alkylthio group
a C_6 - C_{14} arylthio group or
a substituted C_6 - C_{14} arylthio group having at least one of substituents (a) defined below;

or R^1 and R^2, together with the nitrogen atom to which they are attached, form a nitrogen-containing heterocyclic group having from 5 to 8 ring atoms, of which 0 or 1 is an additional nitrogen and/or oxygen and/or sulphur hetero-atom, said heterocyclic group being unsubstituted or having at least one of substituents (b) defined below, or form such a heterocyclic group fused to at least one benzene or naphthalene ring system which ring system is unsubstituted or has at least one of substituents (c) defined below;

one of R^a and R^b represents a hydrogen atom, a C_1 - C_6 alkyl group or a halogen atom, and the other of R^a and R^b represents a group of formula (II):



(II)

R^4 represents a hydrogen atom, a carboxy group, a protected carboxy group or a group of formula $-CONR^8R^9$;
R^5 represents a hydrogen atom, or a carboxyalkyl or protected carboxyalkyl group in which the alkyl part is C_1 - C_6;
n = 0, 1 or 2;
X represents an oxygen or sulphur atom;
R^6 and R^7 are the same or different and each represents:
a hydrogen atom,
a C_1 - C_6 alkyl group,
a C_3 - C_6 alkenyl group,
a C_3 - C_8 cycloalkyl group,
a C_6 - C_{14} aryl group,
a substituted C_6 - C_{14} aryl group having at least one of substituents (c) defined below,
a C_7 - C_{19} aralkyl group,
a substituted C_7 - C_{19} aralkyl group having at least one of substituents (c) defined below,
a C_1 - C_6 alkylsulphonyl group,
a C_1 - C_6 haloalkylsulphonyl group,
a C_6 - C_{14} arylsulphonyl group,
a substituted C_6 - C_{14} arylsulphonyl group having at least one of substituents (c) defined below,
a C_1 - C_{12} alkanoyl group,
a C_4 - C_9 cycloalkylcarbonyl group,
a C_7 - C_{15} arylcarbonyl group or
a substituted C_7 - C_{15} arylcarbonyl group having at least one of substituents (c) defined below;
R^8 and R^9 are the same or different and each represents a hydrogen atom or a C_1 - C_6 alkyl group;

substituents (a):
C_1 - C_6 alkyl groups,
C_1 - C_6 haloalkyl groups,
C_6 - C_{14} aryl groups,
C_7 - C_{19} aralkyl groups,
C_1 - C_{12} alkanoyl groups,
C_7 - C_{15} arylcarbonyl groups,
C_2 - C_7 alkoxycarbonyl groups,
C_7 - C_{15} aryloxycarbonyl groups,
C_8 - C_{20} aralkyloxycarbonyl groups,
groups of formula $-CONR^{10}R^{11}$,
groups of formula $-CSNR^{10}R^{11}$,
(where R^{10} and R^{11} are the same or different and each represents a hydrogen atom, a C_1 - C_6 alkyl group or a C_6 - C_{14} aryl group),
groups of formula $-NR^{12}R^{13}$,
(where R^{12} and R^{13} are the same or different and each represents a hydrogen atom, a C_1 - C_6 alkyl group, a C_6 - C_{14} aryl group, a C_1 - C_6 alkanoyl group or a C_7 - C_{15} arylcarbonyl group),
halogen atoms,
nitro groups,

cyano groups,
hydroxy groups,
C_1 - C_6 alkoxy groups,
C_6 - C_{14} aryloxy groups,
C_1 - C_{12} alkanoyloxy groups,
C_7 - C_{15} arylcarbonyloxy groups,
C_2 - C_7 alkoxycarbonyloxy groups,
C_7 - C_{15} aryloxycarbonyloxy groups,
C_8 - C_{20} aralkyloxycarbonyloxy groups,
carboxy groups,
sulpho groups, and
sulphamoyl groups;

substituents (b):
oxygen atoms,
halogen atoms,
C_1 - C_6 alkyl groups,
C_6 - C_{14} aryl groups,
substituted C_6 - C_{14} aryl groups having at least one of substituents (c) defined below,
C_7 - C_{19} aralkyl groups,
substituted C_7 - C_{19} aralkyl groups having at least one of substituents (c) defined below,
C_1 - C_6 alkanoyl groups,
C_7 - C_{15} arylcarbonyl groups and
substituted C_7 - C_{15} arylcarbonyl groups having at least one of substituents (c) defined below;

substituents (c):
C_1 - C_4 alkyl groups,
C_1 - C_4 alkoxy groups,
C_6 - C_{10} arylgroups,
C_6 - C_{10} aryloxy groups,
C_1 - C_6 alkanoyloxy groups,
halogen atoms,
hydroxy groups,
cyano groups,
trifluoromethyl groups,
carboxy groups, and
nitro groups;
and pharmaceutically acceptable salts and esters thereof.

2. Compounds according to Claim 1, in which:
R^1 and R^2 are the same or different and each represents:
a hydrogen atom,
a C_1 - C_8 alkyl group,
a C_3 - C_6 alkenyl group,
a C_3 - C_8 cycloalkyl group,
a C_6 - C_{14} aryl group,
a substituted C_6 - C_{14} aryl group having at least one of substituents (a^1) defined below,
an aralkyl or substituted aralkyl group with from 1 to 3 aryl parts each of which is C_6 - C_{10} and an alkyl part which is C_1 - C_3, and said substituted aralkyl groups having at least one of substituents (a^1) defined below,
a C_1 - C_6 alkanoyl group,
a benzoyl group,
a substituted benzoyl group having at least one of substituents (a^1) defined below,
a C_2 - C_7 alkoxycarbonyl group,
a group of formula $-CONR^{6'}R^{7'}$,
a group of formula $-CSNR^{6'}R^{7'}$,
a benzenesulphonyl group, or
a toluenesulphonyl group,
or R^1 and R^2, together with the nitrogen atom to which they are attached, form a nitrogen-containing heterocyclic group having 5 or 6 ring atoms, of which 0 or 1 is an additional nitrogen and/or oxygen and/or sulphur hetero-atom, said heterocyclic group being unsubstituted or having at least one of substituents (b^1) defined below, or form such a heterocyclic group fused to at least one benzene ring system which ring system is unsubstituted or has at least one of substituents (c^1) defined below;
$R^{6'}$ and $R^{7'}$ are the same or different and each represents:
a hydrogen atom,
a C_1 - C_6 alkyl group,

a C_3 - C_6 alkenyl group,
a C_3 - C_8 cycloalkyl group,
a C_6 - C_{14} aryl group,
a benzyl group,
a substituted C_6 - C_{14} aryl group having at least one of substituents (c^1) defined below,
a benzenesulphonyl group,
a toluenesulphonyl group,
a C_2 - C_6 alkanoyl groups, or
a C_7 - C_{11} arylcarbonyl group,

substituents (a^1):
C_1 - C_6 alkyl groups,
trifluoromethyl groups,
C_6 - C_{10} aryl groups,
C_7 - C_{12} aralkyl groups,
C_1 - C_6 alkanoyl groups,
C_7 - C_{11} arylcarbonyl groups,
C_2 - C_7 alkoxycarbonyl groups,
groups of formula $-CONR^{10'}R^{11'}$,
groups of formula $-CSNR^{10'}R^{11'}$,
(where $R^{10'}$ and $R^{11'}$ are the same or different and each represents a hydrogen atom, a C_1 - C_6 alkyl group or a C_6 - C_{10} aryl group),
groups of formula $-NR^{12'}R^{13'}$,
(where $R^{12'}$ and $R^{13'}$ are the same or different and each represents a hydrogen atom, a C_1 - C_6 alkyl group, a phenyl group, C_1 - C_6 alkanoyl group or a benzoyl group),
halogen atoms,
nitro groups,
cyano groups,
hydroxy groups,
C_1 - C_6 alkoxy groups,
phenoxy groups,
C_1 - C_6 alkanoyloxy groups,
benzoyloxy groups,
C_2 - C_7 alkoxycarbonyloxy groups, and carboxy groups;

substituents (b^1):
oxygen atoms,
C_1 - C_4 alkyl groups,
phenyl groups,
benzyl groups,
C_1 - C_6 alkanoyl groups, and
benzoyl groups;

substituents (c^1):
C_1 - C_4 alkyl groups,
C_1 - C_4 alkoxy groups,
halogen atoms,
trifluoromethyl groups, and
nitro groups.

3. Compounds according to Claim 1 or Claim 2, in which one of R^a and R^b represents a hydrogen atom, and the other of R^a and R^b represents a group of formula (II), defined in Claim 1.

4. Compounds according to any one of the preceding Claims, in which R^4 represents a hydrogen atom, a C_2 - C_5 alkoxycarbonyl group or a benzyloxycarbonyl group.

5. Compounds according to any one of the preceding Claims, in which R^5 represents a hydrogen atom, a carboxymethyl group or a protected carboxymethyl group, in which the protecting group is a C_1 - C_4 alkyl group, a benzyl group or a group capable of being hydrolyzed in vivo.

6. Compounds according to any one of the preceding Claims, in which n = 0 or 1.

7. Compounds according to any one of the preceding Claims, in which $\overline{X}$ represents a sulphur atom.

8. Compounds according to any one of the preceding Claims, in which R^a represents a hydrogen atom and R^b represents a group of formula (II), as defined in Claim 1.

9. Compounds according to Claim 1, in which:
R^1 and R^2 are the same or different and each represents:
a hydrogen atom,
a C_1 - C_6 alkyl group,
a C_3 - C_6 alkenyl group,

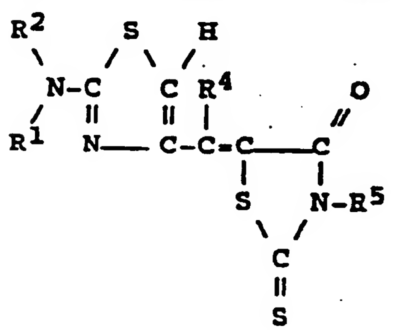
a C_3 - C_8 cycloalkyl group,
a C_6 - C_{14} aryl group,
a substituted C_6 - C_{14} aryl group having at least one of substituents (a^1), defined below,
an aralkyl or substituted aralkyl group with from 1 to 3 aryl parts each of which is C_6 - C_{10} and an alkyl part which is C_1 - C_3, and said substituted aralkyl groups having at least one of substituents (a^1) defined below,
a C_1 - C_6 alkanoyl group,
a benzoyl group,
a substituted benzoyl group having at least one of substituents (a^1) defined below,
a C_2 - C_7 alkoxycarbonyl group,
a group of formula $-CONR^{6'}R^{7'}$,
a group of formula $-CSNR^{6'}R^{7'}$,
a benzenesulphonyl group, or
a toluenesulphonyl group,
or R^1 and R^2, together with the nitrogen atom to which they are attached, form a nitrogen-containing heterocyclic group having 5 or 6 ring atoms, of which 0 or 1 is an additional nitrogen and/or oxygen and/or sulphur hetero-atom, said heterocyclic group being unsubstituted or having at least one of substituents (b^1) defined below, or form such a heterocyclic group fused to at least one benzene ring system which ring system is unsubstituted or has at least one of substituents (c^1) defined below;
one of R^a and R^b represents a hydrogen atom, and the other of R^a and R^b represents a group of formula (II), defined in Claim 1;
R^4 represents a hydrogen atom, a C_2 - C_5 alkoxycarbonyl group or a benzyloxycarbonyl group;
R^5 represents a hydrogen atom, a carboxymethyl group or a protected carboxymethyl group, in which the protecting group is a C_1 - C_4 alkyl group, a benzyl group or a group capable of being hydrolyzed <u>in vivo</u>:
$\underline{n}$ = 0 or 1;
$\underline{X}$ represents a sulphur atom;
$R^{6'}$ and $R^{7'}$ are the same or different and each represents:
a hydrogen atom,
a C_1 - C_6 alkyl group,
a C_3 - C_6 alkenyl group,
a C_3 - C_8 cycloalkyl group,
a C_6 - C_{14} aryl group,
a substituted C_6 - C_{14} aryl group having at least one of substituents (c^1) defined below,
a benzyl group,
a benzenesulphonyl group,
a toluenesulphonyl group,
a C_2 - C_6 alkanoyl group, or
a C_7 - C_{11} arylcarbonyl group,

<u>substituents (a^1):</u>
C_1 - C_6 alkyl groups,
trifluoromethyl groups,
C_6 - C_{10} aryl groups,
C_7 - C_{12} aralkyl groups,
C_1 - C_6 alkanoyl groups,
C_7 - C_{11} arylcarbonyl groups,
C_2 - C_7 alkoxycarbonyl groups,
groups of formula $-CONR^{10'}R^{11'}$,
groups of formula $-CSNR^{10'}R^{11'}$,
(where $R^{10'}$ and $R^{11'}$ are the same or different and each represents a hydrogen atom, a C_1 - C_6 alkyl group or a C_6 - C_{10} aryl group),
groups of formula $-NR^{12'}R^{13'}$,
(where $R^{12'}$ and $R^{13'}$ are the same or different and each represents a hydrogen atom, a C_1 - C_6 alkyl group, a phenyl group, a C_1 - C_6 alkanoyl group or a benzoyl group),
halogen atoms,
nitro groups,
cyano groups,
hydroxy groups,
C_1 - C_6 alkoxy groups,
phenoxy groups,
C_1 - C_6 alkanoyloxy groups,
benzoyloxy groups,
C_2 - C_7 alkoxycarbonyloxy groups, and
carboxy groups;

substituents (b^1):
oxygen atoms,
C_1 - C_4 alkyl groups,
phenyl groups,
benzyl groups,
C_1 - C_8 alkanoyl groups, and
benzoyl groups;

substituents (c^1):
C_1 - C_4 alkyl groups,
C_1 - C_4 alkoxy groups,
halogen atoms,
trifluoromethyl groups, and
nitro groups;
provided that, when R^1 represents said alkanoyl, benzoyl, substituted benzoyl, alkoxycarbonyl, benzenesulphonyl or toluenesulphonyl group or said group of formula $-CONR^{6'}R^{7'}$ or $-CSNR^{6'}R^{7'}$, then R^2 represents said hydrogen atom or said alkyl, alkenyl, cycloalkyl, aryl, substituted aryl, aralkyl or substituted aralkyl group.

10. Compounds according to Claim 1, which are represented by the formula (Ia):



(Ia)

in which:
R^1 and R^2 are the same or different and each represents:
a hydrogen atom,
a C_1 - C_8 alkyl group,
a C_3 - C_8 alkenyl group,
a C_3 - C_8 cycloalkyl group,
a phenyl group,
a naphthyl group,
a substituted phenyl group or a substituted naphthyl group having at least one of substituents (a^2) defined below,
a C_2 - C_8 alkanoyl group,
a C_7 - C_{19} aralkyl group,
a C_7 - C_{19} substituted aralkyl group having at least one of substituents (a^2) defined below,
a benzoyl group,
a substituted benzoyl group having at least one of substituents (a^2) defined below,
a group of formula $-CONR^{6''}R^{7''}$, or
a group of formula $-CSNR^{6''}R^{7''}$,
or R^1 and R^2, together with the nitrogen atom to which they are attached, form a 1-pyrrolidinyl, piperidino, hexamethyleneimino, morpholino, thiomorpholino or 1-piperazinyl group which is unsubstituted or has at least one of substituents (b^2) defined below;
R^4 represents a hydrogen atom or a C_2 - C_5 alkoxycarbonyl group;
R^5 represents a hydrogen atom, a carboxymethyl group or a protected carboxymethyl group, in which the protecting group is a C_1 - C_4 alkyl group, a benzyl group or a group capable of being hydrolyzed in vivo;
$R^{6''}$ and $R^{7''}$ are the same or different and each represents:
a hydrogen atom,
a C_1 - C_8 alkyl group,
an allyl group,
a cyclohexyl group,
a C_6 - C_{10} aryl group,
a substituted C_6 - C_{10} aryl group having at least one of substituents (c^2) defined below,
a benzenesulphonyl group,
a toluenesulphonyl group, or

a benzoyl group.

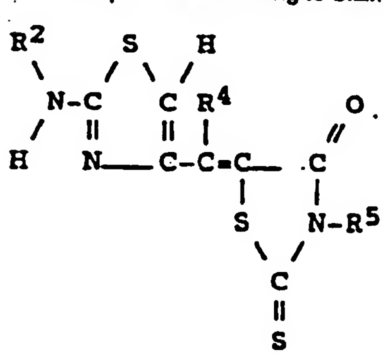
substituents (a^2):
C_1 - C_6 alkyl groups,
trifluoromethyl groups,
phenyl groups,
halogen atoms, and
C_1 - C_6 alkoxy groups;

substituents (b^2):
C_1 - C_4 alkyl groups,
phenyl groups,
benzyl groups,
C_1 - C_6 alkanoyl groups, and
benzoyl groups;

substituents (c^2):
C_1 - C_4 alkyl groups,
C_1 - C_4 alkoxy groups,
halogen atoms,
nitro groups, and
trifluoromethyl groups,
provided that, when R^1 represents a hydrogen atom then R^2 represents a group other than a hydrogen atom, and, when R^1 represents said alkanoyl, benzoyl or substituted benzoyl group or said group of formula -CONR$^{6''}$R$^{7''}$ or -CSNR$^{6''}$R$^{7''}$, then R^2 represents said hydrogen atom or said alkyl, alkenyl, cycloalkyl, phenyl, naphthyl, substituted phenyl, substituted naphthyl, aralkyl or substituted aralkyl group; and pharmaceutically acceptable salts and esters thereof.

11. Compounds according to Claim 10, in which:
R^1 and R^2 are the same or different and each represents:
a hydrogen atom,
a C_1 - C_4 alkyl group,
a C_3 - C_6 alkenyl group,
a C_3 - C_6 cycloalkyl group,
a phenyl group,
a substituted phenyl group having at least one C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen or trifluoromethyl substituent, or
a monoarylcarbamoyl or monoaryl(thiocarbamoyl) group in which the aryl group is a C_6 - C_{10} carbocyclic aryl group which is unsubstituted or has at least one C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen, trifluoromethyl or nitro substituent,
R^4 represents a hydrogen atom or a C_2 - C_5 alkoxycarbonyl group;
R^5 represents a hydrogen atom, a carboxymethyl group or a protected carboxymethyl group, in which the protecting group is a C_1 - C_4 alkyl group, a benzyl group or a group capable of being hydrolyzed in vivo;
provided that, when R^1 represents a hydrogen atom then R^2 represents a group other than a hydrogen atom, and when R^1 represents said monoarylcarbamoyl or monoaryl(thiocarbamoyl) group, then R^2 represents said hydrogen atom or said alkyl, alkenyl, phenyl or substituted phenyl group.

12. Compounds according to Claim 10, which are represented by the formula (Ib):



(Ib)

in which:
R^2 represents a C_1 - C_4 alkyl group, a C_3 - C_6 alkenyl group, a phenyl group, a substituted phenyl group having at least one C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen or trifluoromethyl substituent, or a phenylcarbamoyl or phenyl(thiocarbamoyl) group in each which the phenyl group is unsubstituted or has at least one C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen, trifluoromethyl or nitro substituent,

R^4 represents a hydrogen atom or a C_2 - C_6 alkoxycarbonyl group;
R^5 represents a carboxymethyl group;
and pharmaceutically acceptable salts and esters thereof.

13. 5-{1-Ethoxycarbonyl-1-[2-(3-phenylureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid and pharmaceutically acceptable salts and esters thereof.

14. 5-[2-(3-Phenylureido)thiazol-4-ylmethylene]rhodanine- 3-acetic acid and pharmaceutically acceptable salts and esters thereof.

15. 5-{1-Ethoxycarbonyl-1-[2-[3-(1-naphthyl)ureido]thiazol-4-yl]methylene}rhodanine-3-acetic acid and pharmaceutically acceptable salts and esters thereof.

16. 5-{1-[2-(3-p-Chlorophenylureido)thiazol-4-yl]-1-ethoxycarbonylmethylene}rhodanine-3-acetic acid and pharmaceutically acceptable salts and esters thereof.

17. 5-{1-[2-(3-p-Fluorophenylureido)thiazol-4-yl]-1-ethoxycarbonylmethylene}rhodanine-3-acetic acid and pharmaceutically acceptable salts and esters thereof.

18. 5-{1-Ethoxycarbonyl-1-[2-[3-(4-fluoro-3-nitrophenyl)ureido]thiazol-4-yl]methylene}rhodanine-3-acetic acid and pharmaceutically acceptable salts and esters thereof.

19. 5-{1-Ethoxycarbonyl-1-[2-[3-(2,4,6-trifluorophenyl)ureido]thiazol-4-yl]methylene}rhodanine-3-acetic acid and pharmaceutically acceptable salts and esters thereof.

20. 5-{1-Ethoxycarbonyl-1-[2-(3-phenylthioureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid and pharmaceutically acceptable salts and esters thereof.

21. 5-{1-[2-(3-p-Chlorophenylthioureido)thiazol-4-yl]-1-ethoxycarbonylmethylene}rhodanine-3-acetic acid and pharmaceutically acceptable salts and esters thereof.

22. 5-(2-Ethylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid and pharmaceutically acceptable salts and esters thereof.

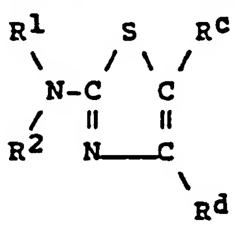
23. 5-(2-Isopropylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid and pharmaceutically acceptable salts and esters thereof.

24. 5-(2-Allylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid and pharmaceutically acceptable salts and esters thereof.

25. 5-(2-Cyclopropylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid and pharmaceutically acceptable salts and esters thereof.

26. A phamaceutical composition for the treatment or prevention of complications of diabetes, which comprises at least one active compound in admixture with a pharmaceutically acceptable carrier or diluent, in which said active compound is a compound according to any one of the preceding Claims.

27. A process for preparing a compound according to any one of Claims 1 to 25, which process comprises the steps:
reacting a compound of formula (III):

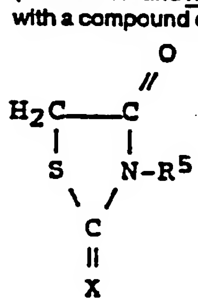


(III)

in which R^1 and R^2 are as defined in Claim 1, and one of R^c and R^d represents a hydrogen atom, a C_1 - C_6 alkyl group or a halogen atom, and the other of R^c and R^d represents a group of formula (IV) :

$$-(CH=CH)_n-\overset{O}{\overset{\|}{C}}-R^4 \qquad (IV)$$

(in which R^4 and n are as defined in Claim 1)
with a compound of formula (V):



(V)

(in which R^5 and X are as defined in Claim 1), and then, if required, converting any group represented by R^1, R^2, R^4 or R^5 to any other such group.

28. The use for the manufacture of a medicament for the treatment of the complications of diabetes of a

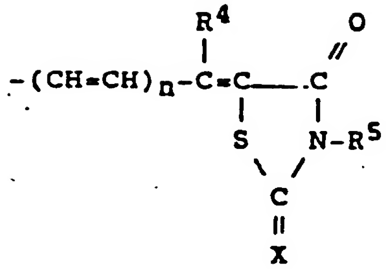
compound according to any one of Claims 1 to 25.

Claims for the following Contracting States: ES, GR:

1. A process for preparing a compound of formula (I):

```
R1      S    Ra
 \     / \  /
  N-C     C
 /  ||    ||           (I)
R2  N_____C
           \
            Rb
```

[in which:
R^1 and R^2 are the same or different and each represents:
a hydrogen atom,
a C_1 - C_{12} alkyl group,
a C_3 - C_6 aliphatic hydrocarbon group having one or two carbon-carbon double or treble bonds,
a C_3 - C_8 cycloalkyl group,
a C_6 - C_{14} aryl group,
a substituted C_6 - C_{14} aryl group having at least one of substituents (a) defined below,
an aralkyl or substituted aralkyl group with from 1 to 3 aryl parts each of which is C_6 - C_{14} and an alkyl part which is C_1 - C_6, and said substituted aralkyl groups having at least one of substituents (a) defined below,
a C_1 - C_{12} alkanoyl group,
a C_3 - C_{12} alkenoyl group,
a C_4 - C_9 cycloalkylcarbonyl group,
a C_7 - C_{15} arylcarbonyl group,
a substituted C_7 - C_{15} arylcarbonyl group having at least one of substituents (a) defined below,
an arylalkanoyl group in which the aryl part is C_6 - C_{14} and is unsubstituted or has at least one of substituents (a) defined below and the alkanoyl part is C_2 - C_6,
an arylalkenoyl group in which the aryl part is C_6 - C_{14} and is unsubstituted or has at least one of substituents (a) defined below and the alkenoyl part is C_3 - C_6,
a C_2 - C_7 alkoxycarbonyl group,
a C_7 - C_{15} aryloxycarbonyl group,
a substituted C_7 - C_{15} aryloxycarbonyl group having at least one of substituents (a) defined below,
a C_8 - C_{20} aralkyloxycarbonyl group,
a substituted C_8 - C_{20} aralkyloxycarbonyl group having at least one of substituents (a) defined below,
a group of formula $-CONR^6R^7$,
a group of formula $-CSNR^6R^7$,
a C_1 - C_6 alkylsulphonyl group,
a C_1 - C_6 haloalkylsulphonyl group,
a C_6 - C_{14} arylsulphonyl group,
a substituted C_6 - C_{14} arylsulphonyl group having at least one of substituents (a) defined below,
a C_1 - C_6 alkylthio group,
a C_6 - C_{14} arylthio group or
a substituted C_6 - C_{14} arylthio group having at least one of substituents (a) defined below;
or R^1 and R^2, together with the nitrogen atom to which they are attached, form a nitrogen-containing heterocyclic group having from 5 to 8 ring atoms, of which 0 or 1 is an additional nitrogen and/or oxygen and/or sulphur hetero-atom, said heterocyclic group being unsubstituted or having at least one of substituents (b) defined below, or form such a heterocyclic group fused to at least one benzene or naphthalene ring system which ring system is unsubstituted or has at least one of substituents (c) defined below;
one of R^a and R^b represents a hydrogen atom, a C_1 - C_6 alkyl group or a halogen atom, and the other of R^a and R^b represents a group of formula (II):



(II)

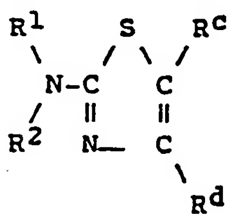
R^4 represents a hydrogen atom, a carboxy group, a protected carboxy group or a group of formula $-CONR^8R^9$;
R^5 represents a hydrogen atom, or a carboxyalkyl or protected carboxyalkyl group in which the alkyl part is $C_1 - C_6$;
$\underline{n} = 0, 1$ or 2;
$\underline{X}$ represents an oxygen or sulphur atom;
R^6 and R^7 are the same or different and each represents:
a hydrogen atom,
a $C_1 - C_6$ alkyl group,
a $C_3 - C_6$ alkenyl group,
a $C_3 - C_8$ cycloalkyl group,
a $C_6 - C_{14}$ aryl group,
a substituted $C_6 - C_{14}$ aryl group laving at least one of substituents (c) defined below,
a $C_7 - C_{19}$ aralkyl group,
a substituted $C_7 - C_{19}$ aralkyl group having at least one of substituents (c) defined below,
a $C_1 - C_6$ alkylsulphonyl group,
a $C_1 - C_6$ haloalkylsulphonyl group,
a $C_6 - C_{14}$ arylsulphonyl group,
a substituted $C_6 - C_{14}$ arylsulphonyl group having at least one of substituents (c) defined below,
a $C_1 - C_{12}$ alkanoyl group,
a $C_4 - C_9$ cycloalkylcarbonyl group,
a $C_7 - C_{15}$ arylcarbonyl group, or
a substituted $C_7 - C_{15}$ arylcarbonyl group having at least one of substituents (c) defined below;
R^8 and R^9 are the same or different and each represents a hydrogen atom or a $C_1 - C_6$ alkyl group;

<u>substituents (a):</u>
$C_1 - C_6$ alkyl groups,
$C_1 - C_6$ haloalkyl groups,
$C_6 - C_{14}$ aryl groups,
$C_7 - C_{19}$ aralkyl groups,
$C_1 - C_{12}$ alkanoyl groups,
$C_7 - C_{15}$ arylcarbonyl groups,
$C_2 - C_7$ alkoxycarbonyl groups,
$C_7 - C_{15}$ aryloxycarbonyl groups,
$C_8 - C_{20}$ aralkyloxycarbonyl groups,
groups of formula $-CONR^{10}R^{11}$,
groups of formula $-CSNR^{10}R^{11}$,
(where R^{10} and R^{11} are the same or different and each represents a hydrogen atom, a $C_1 - C_6$ alkyl group or a $C_6 - C_{14}$ aryl group),
groups of formula $-NR^{12}R^{13}$,
(where R^{12} and R^{13} are the same or different and each represents a hydrogen atom, a $C_1 - C_6$ alkyl group, a $C_6 - C_{14}$ aryl group, a $C_1 - C_6$ alkanoyl group or a $C_7 - C_{15}$ arylcarbonyl group),
halogen atoms,
nitro groups,
cyano groups,
hydroxy groups,
$C_1 - C_6$ alkoxy groups,
$C_6 - C_{14}$ aryloxy groups,
$C_1 - C_{12}$ alkanoyloxy groups,
$C_7 - C_{15}$ arylcarbonyloxy groups,
$C_2 - C_7$ alkoxycarbonyloxy groups,
$C_7 - C_{15}$ aryloxycarbonyloxy groups,
$C_8 - C_{20}$ aralkyloxycarbonyloxy groups,

carboxy groups,
sulpho groups, and
sulphamoyl groups;

<u>substituents (b):</u>
oxygen atoms,
halogen atoms,
C_1 - C_6 alkyl groups,
C_6 - C_{14} aryl groups,
substituted C_6 - C_{14} aryl groups having at least one of substituents (c) defined below,
C_7 - C_{19} aralkyl groups,
substituted C_7 - C_{19} aralkyl groups having at least one of substituents (c) defined below,
C_1 - C_6 alkanoyl groups,
C_7 - C_{15} arylcarbonyl groups and
substituted C_7 - C_{15} arylcarbonyl groups having at least one of substituents (c) defined below;

<u>substituents (c):</u>
C_1 - C_4 alkyl groups,
C_1 - C_4 alkoxy groups,
C_6 - C_{10} aryl groups,
C_6 - C_{10} aryloxy groups,
C_1 - C_6 alkanoyloxy groups, halogen atoms,
hydroxy groups,
cyano groups,
trifluoromethyl groups,
carboxy groups, and
nitro groups];
or a pharmaceutically acceptable salt or ester thereof, which process comprises the steps:
reacting a compound of formula (III):

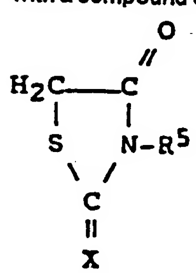


(III)

in which R^1 and R^2 are as defined above, and one of R^c and R^d represents a hydrogen atom, a C_1 - C_6 alkyl group or a halogen atom, and the other of R^c and R^d represents a group of formula (IV):

$-(CH=CH)_n-\overset{O}{\overset{\|}{C}}-R^4$ (IV)

(in which R^4 and <u>n</u> are as defined above)
with a compound of formula (V):



(V)

(in which R^5 and X are as defined above), and then, if required, converting any group represented by R^1, R^2, R^4 or R^5 to any other such group.

2. A process according to Claim 1, in which:
R^1 and R^2 are the same or different and each represents:
a hydrogen atom,
a C_1 - C_8 alkyl group,
a C_3 - C_6 alkenyl group,
a C_3 - C_8 cycloalkyl group,
a C_6 - C_{14} aryl group,

a substituted C_6 - C_{14} aryl group having at least one of substituents (a^1) defined below,
an aralkyl or substituted aralkyl group with from 1 to 3 aryl parts each of which is C_6 - C_{10} and an alkyl part which is C_1 - C_3, and said substituted aralkyl groups having at least one of substituents (a^1) defined below,
a C_1 - C_6 alkanoyl group,
a benzoyl group,
a substituted benzoyl group having at least one of substituents (a^1) defined below,
a C_2 - C_7 alkoxycarbonyl group,
a group of formula $CONR^{6'}R^{7'}$,
a group of formula $CSNR^{6'}R^{7'}$,
a benzenesulphonyl group, or
a toluenesulphonyl group,
or R^1 and R^2, together with the nitrogen atom to which they are attached, form a nitrogen-containing heterocyclic group having 5 or 6 ring atoms, of which 0 or 1 is an additional nitrogen and/or oxygen and/or sulphur hetero-atom, said heterocyclic group being unsubstituted or having at least one of substituents (b^1) defined below, or form such a heterocyclic group fused to at least one benzene ring system which ring system is unsubstituted or has at least one of substituents (c^1) defined below;
$R^{6'}$ and $R^{7'}$ are the same or different and each represents:
a hydrogen atom,
a C_1 - C_6 alkyl group,
a C_3 - C_6 alkenyl group,
a C_3 - C_8 cycloalkyl group,
a C_6 - C_{14} aryl group,
a benzyl group,
a substituted C_6 - C_{14} aryl group having at least one of substituents (c^1) defined below,
a benzenesulphonyl group,
a toluenesulphonyl group,
a C_2 - C_6 alkanoyl groups, and a C_7 - C_{11} arylcarbonyl group.

substituents (a^1):
C_1 - C_6 alkyl groups,
trifluoromethyl groups,
C_6 - C_{10} aryl groups,
C_7 - C_{12} aralkyl groups,
C_1 - C_6 alkanoyl groups,
C_7 - C_{11} arylcarbonyl groups,
C_2 - C_7 alkoxycarbonyl groups,
groups of formula $-CONR^{10'}R^{11'}$,
groups of formula $-CSNR^{10'}R^{11'}$,
(where $R^{10'}$ and $R^{11'}$ are the same or different and each represents a hydrogen atom, a C_1 - C_6 alkyl group or a C_6 - C_{10} aryl group),
groups of formula $-NR^{12'}R^{13'}$,
(where $R^{12'}$ and $R^{13'}$ are the same or different and each represents a hydrogen atom, a C_1 - C_6 alkyl group, a phenyl group, C_1 - C_6 alkanoyl group or a benzoyl group),
halogen atoms,
nitro groups,
cyano groups,
hydroxy groups,
C_1 - C_6 alkoxy groups,
phenoxy groups,
C_1 - C_6 alkanoyloxy groups,
benzoyloxy groups,
C_2 - C_7 alkoxycarbonyloxy groups, and
carboxy groups;

substituents (b^1):
oxygen atoms,
C_1 - C_4 alkyl groups,
phenyl groups,
benzyl groups,
C_1 - C_6 alkanoyl groups, and
benzoyl groups;

substituents (c^1):
C_1 - C_4 alkyl groups,
C_1 - C_4 alkoxy groups,
halogen atoms,
trifluoromethyl groups, and
nitro groups.

3. A process according to Claim 1 or Claim 2, in which one of R^a and R^b represents a hydrogen atom, and the other of R^a and R^b represents a group of formula (II), defined in Claim 1.

4. A process according to any one of the preceding Claims, in which R^4 represents a hydrogen atom, a C_2 - C_6 alkoxycarbonyl group or a benzyloxycarbonyl group.

5. A process according to any one of the preceding Claims, in which R^5 represents a hydrogen atom, a carboxymethyl group or a protected carboxymethyl group, in which the protecting group is a C_1 - C_4 alkyl group, a benzyl group or a group capable of being hydrolyzed in vivo.

6. A process according to any one of the preceding Claims, in which $n = 0$ or 1.

7. A process according to any one of the preceding Claims, in which $\overline{X}$ represents a sulphur atom.

8. A process according to any one of the preceding Claims, in which R^a represents a hydrogen atom and R^b represents a group of formula (II), as defined in Claim 1.

9. A process according to Claim 1, in which:
R^1 and R^2 are the same or different and each represents:
a hydrogen atom,
a C_1 - C_8 alkyl group,
a C_3 - C_6 alkenyl group,
a C_3 - C_8 cycloalkyl group,
a C_6 - C_{14} aryl group,
a substituted C_6 - C_{14} aryl group having at least one of substituents (a^1) defined below,
an aralkyl or substituted aralkyl group with from 1 to 3 aryl parts each of which is C_6 - C_{10} and an alkyl part which is C_1 - C_3, and said substituted aralkyl groups having at least one of substituents (a^1) defined below,
a C_1 - C_6 alkanoyl group,
a benzoyl group,
a substituted benzoyl group having at least one of substituents (a^1) defined below,
a C_2 - C_7 alkoxycarbonyl group,
a group of formula $-CONR^{6'}R^{7'}$,
a group of formula $-CSNR^{6'}R^{7'}$,
a benzenesulphonyl group, or
a toluenesulphonyl group,
or R^1 and R^2, together with the nitrogen atom to which they are attached, form a nitrogen-containing heterocyclic group having 5 or 6 ring atoms, of which 0 or 1 is an additional nitrogen and/or oxygen and/or sulphur hetero-atom, said heterocyclic group being unsubstituted or having at least one of substituents (b^1) defined below, or form such a heterocyclic group fused to at least one benzene ring system which ring system is unsubstituted or has at least one of substituents (c^1) defined below;
one of R^a and R^b represents a hydrogen atom, and the other of R^a and R^b represents a group of formula (II), defined in Claim 1;
R^4 represents a hydrogen atom, a C_2 - C_6 alkoxycarbonyl group or a benzyloxycarbonyl group;
R^5 represents a hydrogen atom, a carboxymethyl group or a protected carboxymethyl group, in which the protecting group is a C_1 - C_4 alkyl group, a benzyl group or a group capable of being hydrolyzed in vivo;
$n = 0$ or 1;
$\overline{X}$ represents a sulphur atom;
$R^{6'}$ and $R^{7'}$ are the same or different and each represents:
a hydrogen atom,
a C_1 - C_6 alkyl group,
a C_3 - C_6 alkenyl group,
a C_3 - C_8 cycloalkyl group,
a C_6 - C_{14} aryl group,
a substituted C_6 - C_{14} aryl group having at least one of substituents (c^1) defined below,
a benzyl group,
a benzenesulphonyl group,
a toluenesulphonyl group,
a C_2 - C_6 alkanoyl group, or
a C_7 - C_{11} arylcarbonyl group,

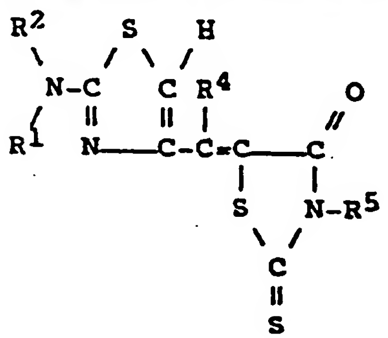
substituents (a^1):
C_1 - C_6 alkyl groups,
trifluoromethyl groups,
C_6 - C_{10} aryl groups,

C_7 - C_{12} aralkyl groups,
C_1 - C_6 alkanoyl groups,
C_7 - C_{11} arylcarbonyl groups,
C_2 - C_7 alkoxycarbonyl groups,
groups of formula -CONR$^{10'}$R$^{11'}$,
groups of formula -CSNR$^{10'}$R$^{11'}$,
(where R$^{10'}$ and R$^{11'}$ are the same or different and each represents a hydrogen atom, a C_1 - C_6 alkyl group or a C_6 - C_{10} aryl group),
groups of formula -NR$^{12'}$R$^{13'}$,
(where R$^{12'}$ and R$^{13'}$ are the same or different and each represents a hydrogen atom, a C_1 - C_6 alkyl group, a phenyl group, a C_1 - C_6 alkanoyl group or a benzoyl group),
halogen atoms,
nitro groups,
cyano groups,
hydroxy groups,
C_1 - C_6 alkoxy groups,
phenoxy groups,
C_1 - C_6 alkanoyloxy groups,
benzoyloxy groups,
C_2 - C_7 alkoxycarbonyloxy groups, and carboxy groups;

substituents (b^1):
oxygen atoms,
C_1 - C_4 alkyl groups,
phenyl groups,
benzyl groups,
C_1 - C_6 alkanoyl groups, and
benzoyl groups;

substituents (c^1):
C_1 - C_4 alkyl groups,
C_1 - C_4 alkoxy groups,
halogen atoms,
trifluoromethyl groups, and
nitro groups;
provided that, when R^1 represents said alkanoyl, benzoyl, substituted benzoyl, alkoxycarbonyl, benzenesulphonyl or toluenesulphonyl group or said group of formula -CONR$^{6'}$R$^{7'}$ or -CSNR$^{6'}$R$^{7'}$, then R^2 represents said hydrogen atom or said alkyl, alkenyl, cycloalkyl, aryl, substituted aryl, aralkyl or substituted aralkyl group.

10. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (Ia):



(Ia)

in which:
R^1 and R^2 are the same or different and each represents:
a hydrogen atom,
a C_1 - C_6 alkyl group,
a C_3 - C_6 alkenyl group,
a C_3 - C_6 cycloalkyl group,
a phenyl group,
a naphthyl group,
a substituted phenyl group or a substituted naphthyl group having at least one of substituents (a^2) defined below,

a C_2 - C_6 alkanoyl group;
a C_7 - C_{10} aralkyl group,
a C_7 - C_{10} substituted aralkyl group having at least one of substituents (a^2) defined below,
a benzoyl group,
a substituted benzoyl group having at least one of substituents (a^2) defined below,
a group of formula $-CONR^{6''}R^{7''}$, or
a group of formula $-CSNR^{6''}R^{7''}$,
or R^1 and R^2, together with the nitrogen atom to which they are attached, form a 1-pyrrolidinyl, piperidino, hexamethyleneimino, morpholino, thiomorpholino or 1-piperazinyl group which is unsubstituted or has at least one of substituents (b^2) defined below;
R^4 represents a hydrogen atom or a C_2 - C_6 alkoxycarbonyl group;
R^5 represents a hydrogen atom, a carboxymethyl group or a protected carboxymethyl group, in which the protecting group is a C_1 - C_4 alkyl group, a benzyl group or a group capable of being hydrolyzed in vivo;
$R^{6''}$ and $R^{7''}$ are the same or different and each represents:
a hydrogen atom,
a C_1 - C_6 alkyl group,
an allyl group,
a cyclohexyl group,
a C_6 - C_{10} aryl group,
a substituted C_6 - C_{10} aryl group having at least one of substituents (c^2) defined below,
a benzenesulphonyl group,
a toluenesulphonyl group, or
a benzoyl group,

substituents (a^2):
C_1 - C_6 alkyl groups,
trifluoromethyl groups,
phenyl groups,
halogen atoms, and
C_1 - C_6 alkoxy groups;

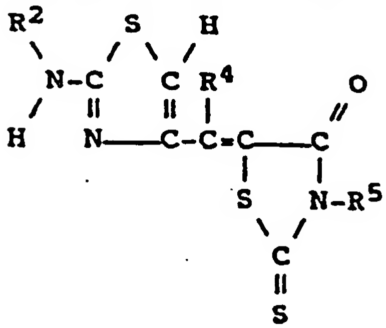
substituents (b^2):
C_1 - C_4 alkyl groups,
phenyl groups,
benzyl groups,
C_1 - C_6 alkanoyl groups, and
benzoyl groups;

substituents (c^2):
C_1 - C_4 alkyl groups,
C_1 - C_4 alkoxy groups,
halogen atoms,
nitro groups, and
trifluoromethyl groups;
provided that, when R^1 represents a hydrogen atom then R^2 represents a group other than a hydrogen atom, and, when R^1 represents said alkanoyl, benzoyl or substituted benzoyl group or said group of formula $-CONR^{6''}R^{7''}$ or $-CSNR^{6''}R^{7''}$, then R^2 represents said hydrogen atom or said alkyl, alkenyl, cycloalkyl, phenyl, naphthyl, substituted phenyl, substituted naphthyl, aralkyl or substituted aralkyl group; or a pharmaceutically acceptable salt or ester thereof.

11. A process according to Claim 10, in which:
R^1 and R^2 are the same or different and each represents:
a hydrogen atom,
a C_1 - C_4 alkyl group,
a C_3 - C_6 alkenyl group,
a C_3 - C_6 cycloalkyl group,
a phenyl group,
a substituted phenyl group having at least one C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen or trifluoromethyl substituent, or
a monoarylcarbamoyl or monoaryl(thiocarbamoyl) group in which the aryl group is a C_6 - C_{10} carbocyclic aryl group which is unsubstituted or has at least one C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen, trifluoromethyl or nitro substituent,
R^4 represents a hydrogen atom or a C_2 - C_6 alkoxycarbonyl group;
R^5 represents a hydrogen atom, a carboxymethyl group or a protected carboxymethyl group, in which the protecting group is a C_1 - C_4 alkyl group, a benzyl group or a group capable of being hydrolyzed in vivo;
provided that, when R^1 represents a hydrogen atom then R^2 represents a group other than a hydrogen

atom, and, when R^1 represents said monoarylcarbamoyl or monoaryl(thiocarbamoyl) group, then R^2 represents said hydrogen atom or said alkyl, alkenyl, phenyl or substituted phenyl group.

12. A process according to Claim 10, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (Ib):



(Ib)

in which:

R^2 represents a C_1 - C_4 alkyl group, a C_3 - C_6 alkenyl group, a phenyl group, a substituted phenyl group having at least one C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen or trifluoromethyl substituent, or a phenylcarbamoyl or phenyl(thiocarbamoyl) group in each which the phenyl group is unsubstituted or has at least one C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen, trifluoromethyl or nitro substituent,

R^4 represents a hydrogen atom or a C_2 -C_5 alkoxycarbonyl group;

R^5 represents a carboxymethyl group;

or a pharmaceutically acceptable salt or ester thereof.

13. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare:

5-{1-ethoxycarbonyl-1-[2-(3-phenylureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid;
5-[2-(3-phenylureido)thiazol-4-ylmethylene]rhodanine-3-acetic acid;
5-{1-ethoxycarbonyl-1-[2-[3-(1-naphthyl)ureido]thiazol-4-yl]methylene}rhodanine-3-acetic acid;
5-{1-[2-(3-p-chlorophenylureido)thiazol-4-yl]-1-ethoxycarbonylmethylene}rhodanine-3-acetic acid;
5-{1-[2-(3-p-fluorophenylureido)thiazol-4-yl]-1-ethoxycarbonylmethylene}rhodanine-3-acetic acid;
5-{1-ethoxycarbonyl-1-[2-[3-(4-fluoro-3-nitrophenyl)ureido]thiazol-4-yl]methylene}rhodanine-3-acetic acid;
5-{1-ethoxycarbonyl-1-[2-[3-(2,4,6-trifluorophenyl)ureido]thiazol-4-yl]methylene}rhodanine-3-acetic acid;
5-{1-ethoxycarbonyl-1-[2-(3-phenylthioureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid;
5-{1-[2-(3-p-chlorophenylthioureido)thiazol-4-yl]-1-ethoxycarbonylmethylene}rhodanine-3-acetic acid;
5-(2-ethylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid;
5-(2-isopropylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid;
5-(2-allylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid;
5-(2-cyclopropylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid;
or a pharmaceutically acceptable salt or ester thereof.

14. A process for preparing a pharmaceutical composition for the treatment or prevention of complications of diabetes, by mixing at least one active compound with a pharmaceutically acceptable carrier or diluent, in which said active compound is a compound according to any one of the preceding Claims.

15. The use for the manufacture of a medicament for the treatment of the complications of diabetes of a compound of formula (I) or a pharmaceutically acceptable salt or ester thereof, as defined in any one of Claims 1 to 12.

16. The use according to Claim 15, in which said compound is:

5-{1-ethoxycarbonyl-1-[2-(3-phenylureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid;
5-[2-(3-phenylureido)thiazol-4-ylmethylene]rhodanine-3-acetic acid;
5-{1-ethoxycarbonyl-1-[2-[3-(1-naphthyl)ureido]thiazol-4-yl]methylene}rhodanine-3-acetic acid;
5-{1-[2-(3-p-chlorophenylureido)thiazol-4-yl]-1-ethoxycarbonylmethylene}rhodanine-3-acetic acid;
5-{1-[2-(3-p-fluorophenylureido)thiazol-4-yl]-1-ethoxycarbonylmethylene}rhodanine-3-acetic acid;
5-{1-ethoxycarbonyl-1-[2-[3-(4-fluoro-3-nitrophenyl) ureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid;
5-{1-ethoxycarbonyl-1-[2-[3-(2,4,6-trifluorophenyl)ureido]thiazol-4-yl]methylene}rhodanine-3-acetic acid;
5-{1-ethoxycarbonyl-1-[2-(3-phenylthioureido)thiazol-4-yl]methylene}rhodanine-3-acetic acid;
5-{1-[2-(3-p-chlorophenylthioureido)thiazol-4-yl]-1-ethoxycarbonylmethylene}rhodanine-3-acetic acid;
5-(2-ethylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid;
5-(2-isopropylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid;
5-(2-allylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid;
5-(2-cyclopropylaminothiazol-4-ylmethylene)rhodanine-3-acetic acid;

or a pharmaceutically acceptable salt or ester thereof.